The New England
Journal of Medicine

Copyright, 1952, by the Massachusetts Medical Society

Volume 246 MARCH 20, 1952 Number 12

MULTIPLE-BALLOON-KYMOGRAPH RECORDING OF THE EFFECT OF BANTHINE, BELLADONNA AND PLACEBOS ON UPPER-INTESTINAL MOTILITY*

WILLIAM P. CHAPMAN, M.D.,† ARTHUR B. FRENCH, M.D.,‡ PHYLLIS S. HOFFMAN,§ AND CHESTER M. JONES, M.D.¶

BOSTON

RECENT studies have demonstrated that Banthine, β-diethylaminoethyl xanthine-9-carboxylate methobromide, has a definite action on gastrointestinal function. This new drug acts chiefly as a blocking agent on the parasympathetic nervous system and, to a lesser degree, on the sympathetic nervous system.[1] In dosages in the toxic range it exerts a curare-like action on skeletal muscle. In man, Banthine has been found to retard gastric emptying, decrease contractions of the small and large intestine and diminish the volume of gastric secretion.[2-4] When administered therapeutically, present observations indicate that Banthine is effective in the treatment of patients with peptic ulcer and in certain disturbances of the gastrointestinal tract that are manifested by hypermotility.[5-9] The purpose of this study was to compare the action of orally administered Banthine with that of tincture of belladonna and placebos on the motility of the upper small intestine in healthy adult men. The subjects were all college students with an age range of from nineteen to twenty-four years. They were divided into two groups. Group I consisted of 5 subjects who had four tests each — one with tincture of belladonna, 0.4 cc. or 20 drops; one with a placebo given orally; one with Banthine, 100 mg., given orally; and one test with tincture of belladonna, 0.6 cc. or 30 drops, given in the same sequence. Group II consisted of 26 subjects who had nine tests with Banthine, 100 mg., given orally; nine with tincture of belladonna, 0.4 cc., and 20 with placebos administered orally.|| Eighteen subjects had one test; 5 subjects had two tests; 2 subjects had three tests; and 1 subject had four tests. None of these subjects were tested with all 3 agents.

*From the Medical Services, Massachusetts General Hospital, and the Department of Medicine, Harvard Medical School.
Supported by a grant from G. D. Searle and Company, Chicago, Illinois.

†Instructor in medicine, Harvard Medical School; assistant in medicine, Massachusetts General Hospital.

‡Formerly, assistant in medicine, Massachusetts General Hospital, and clinical and research fellow, Harvard Medical School; instructor in medicine, University of Utah College of Medicine.

§Formerly, technician, Massachusetts General Hospital.

¶Clinical professor of medicine, Harvard Medical School; physician, Massachusetts General Hospital.

||The results of the 9 belladonna tests and of 14 of the placebo tests have been reported elsewhere.[11]

METHOD

The multiple-balloon-kymograph recording method, the evaluation of the tracings and the test procedure have been described.[10, 11] In brief, the subjects reported without breakfast to the laboratory at 8:30 a.m. and remained in a fasting state until the completion of the test in the afternoon. The balloons were placed in the upper small intestine under fluoroscopic control. In Group I subjects the three distal balloons were placed in the duodenum and upper jejunum, the proximal balloon in the stomach. In Group II subjects one test was run with one balloon in the duodenum, five tests with two balloons in the duodenum, 29 tests with three balloons in the duodenum and upper jejunum and three tests with all four balloons in the duodenum and upper jejunum. A recording was made of the motility for a minimal control period of forty-five minutes. The agent was then administered orally without the subject's knowledge of its content. Verbal suggestion was not used. After the agent was administered, the recording was continued for four hours in the Group I tests and for from forty-five minutes to four hours in the Group II tests. Changes in the amplitude and frequency of propulsive contractions were assessed by visual inspection. Total contractions (propulsive and nonpropulsive) and "tone," or the sustained tension of the bowel wall, were determined by measurements of the surface areas beneath the tracings at five-minute levels previous to each fifteen-minute period by a polar planimeter. In addition, the average tone levels per five-minute period, during spasm-free intervals, were measured by a centimeter ruler throughout the test period. The effects of the agents on contractions and tone were compared at each fifteen-minute interval with the average level of activity during the last forty-five minutes prior to the administration of the agents. In Group I subjects, additional observations made at fifteen-minute in-

tervals included recording of blood pressure and heart rate; measurement of pupillary size by a standardized technic employing a calibrated scale; and questioning the subject about symptoms, including specific questions concerning dryness of the mouth. In Group II subjects similar data were obtained but are not included in this report, as they were insufficiently completed.

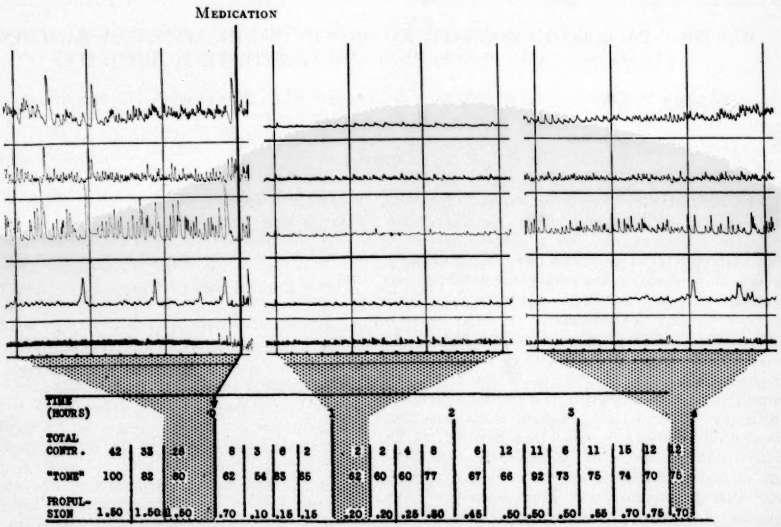


FIGURE 1. *Three Sections of Graphic Recording, with Numbers Below Tracing Indicating Levels of Total Contractions, Tone and Propulsion for Each Fifteen-Minute Period Before and After the Oral Administration of 100 Mg. of Banthine. The first tracing is from the upper jejunum, the second from the distal duodenum or upper jejunum and the third from the duodenum. The fourth, or stomach tracing, was not used in the calculation. The vertical lines in the graph indicate time at five-minute intervals. The level of total contractions (propulsion and nonpropulsion) and tone were measured for five minutes previous to each fifteen-minute period and were expressed in square centimeters of surface area of the tracing. Propulsion values represent the average level per fifteen-minute period and were expressed in arbitrary units. The figure shows within fifteen minutes after the administration of Banthine a striking decrease in total contractions and propulsion, with a less marked diminution in tone. About 135 minutes later intestinal motility had recovered partially but continued to remain well below the control level for the remainder of the observation period, as shown in the graphic record. As indicated by the shaded columns, the sections of the graphic record were for fifteen minutes just prior to drug administration and at intervals of sixty to seventy-five and 225-240 minutes after the administration of Banthine. The bottom tracing indicates respirations.*

RESULTS

Three sections of a graphic record, illustrating the effect of Banthine, 100 mg., on the motility of the upper small intestine (duodenum and upper jejunum) are shown in Figure 1. The numerical values below the tracings indicate the changes in total contractions (propulsive and nonpropulsive), tone and propulsion for each fifteen-minute period before and after the medication was given. The values show that within fifteen minutes after oral administration of Banthine there was a striking decrease in total contractions and propulsion and a less pronounced decline in tone. The diminution in contractions became more marked fifteen minutes later and the effect was maintained for the next seventy-five minutes. Thereafter, contractile activity recovered partially but continued to remain well below the control levels for the remainder of the four-hour post-medication period. Except for the 165-minute post-drug interval, tone remained slightly decreased. A similar tracing including numerical values of changes in activity has been reported for tincture of belladonna, 0.4 cc.[11]

The summary data for the changes in propulsive contractions, total contractions and tone will be presented separately for the two groups of subjects.

Propulsive Contractions

Group I subjects. Figure 2 shows that in the 5 subjects in Group I who received all the agents Banthine, 100 mg., caused more than twice as great a decrease in propulsive contractions at the thirty- and forty-five-minute post-medication intervals as

did tincture of belladonna in either the 0.4-cc. or 0.6-cc. dosage. For the next ninety minutes Banthine was only slightly more active than belladonna in either dosage. Thereafter, little difference was observed in the effect of belladonna, 0.6 cc., and Banthine, although tincture of belladonna, 0.4 cc., showed only slightly more effect than did the placebos. Prior to the 150-minute post-medication period it was clear that the action of Banthine and tincture

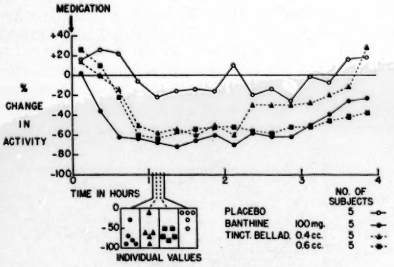


FIGURE 2. *Effect of Banthine, Tincture of Belladonna and Placebos on Propulsive Contractions in Group I Subjects.*

The figure shows that both Banthine, 100 mg., and tincture of belladonna in dosages of 0.4 cc. and 0.6 cc. caused a more striking decrease in propulsive contractions than was noted after placebo administration. Banthine acted sooner and for the first two hours of the post-medication period caused a slightly greater decrease in activity. During the remaining two hours there was very little difference between the activity noted with belladonna, 0.6 cc., and Banthine, whereas belladonna, 0.4 cc., appeared to have a slightly more sustained effect than did the placebos. The black dots (Banthine values), the black squares (0.6 cc., belladonna values), the black triangles (0.4-cc.-tincture-of-belladonna values) and the open dots (placebo values) indicate the mean of the sum of the percentage changes in activity for each subject for each fifteen-minute period, compared to the last forty-five minutes of the control period. The individual variation for the post-medication interval of sixty to seventy-five minutes is shown by the scattergram.

of belladonna in both dosages caused a much greater decline in propulsive activity than was noted after the administration of placebos. The individual variation in activity at the sixty-to-seventy-five-minute post-medication period is shown by the scattergram. The range of the variation was slightly less for the placebos and tincture of belladonna, 0.6 cc., than for Banthine and tincture of belladonna, 0.4 cc.

Group II subjects. Figure 3 shows that Banthine, 100 mg., was much more active than tincture of belladonna, 0.4 cc., for the first sixty minutes of the post-medication period. For the next sixty minutes Banthine continued to be more effective than belladonna, though to a lesser degree. Thereafter the differences between the two drugs were less striking. The decline in contractions following placebo administration averaged about 25 per cent, as compared to 70 to 75 per cent for Banthine and tincture of belladonna. As shown by the scattergram for the sixty-to-seventy-five-minute post-medication period, the range of variation of individual values was about the same for the two drugs — that is, from −10 to −95 per cent as compared to + 40 to −85 per cent for the placebo tests.

Total Contractions

Group I subjects. As shown in Figure 4, Banthine caused a greater decrease in total contractions (propulsive and nonpropulsive) during the thirty- and forty-five-minute post-medication period than did tincture of belladonna in either dosage. At the sixty-minute post-medication period, Banthine and tincture of belladonna, 0.4 cc., both caused more than a 70 per cent decrease in contractions as compared to a 35 per cent decrease in activity after the administration of tincture of belladonna, 0.6 cc. Fifteen

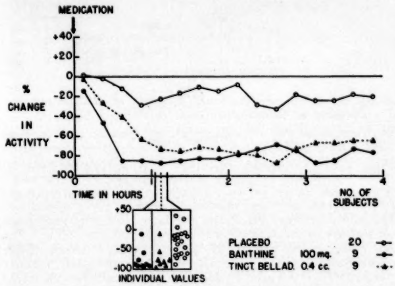


FIGURE 3. *Effect of Banthine, Tincture of Belladonna and Placebos on Propulsive Contractions in Group II Subjects.*

The figure shows that tincture of belladonna, 0.4 cc., and Banthine, 100 mg., diminished propulsive contractions to a much greater extent than was noted after placebo administration. Banthine acted more rapidly and produced a somewhat more striking decrease in propulsive contractions than did belladonna, 0.4 cc., during the first 120 minutes of the observation period. During the next hour both drugs showed about the same activity. During the last hour of the observation period, Banthine appeared to have a somewhat greater effect. The individual variation for the agents during the sixty-to-seventy-five minute post-medication interval is shown by the scattergram. The symbols indicating the agents used and the method of determining the percentage changes in activity for each fifteen-minute period were the same as described in Figure 2. The number of subjects included in each drug study at the end of each sixty-minute post-medication period was as follows: at sixty minutes, Banthine 9, belladonna 8, placebos 20; at 120 minutes, Banthine 9, belladonna 7, placebos 19; at 180 minutes, Banthine 7, belladonna 5, placebos 13; at 240 minutes, Banthine 3, belladonna 5, placebos 8.

minutes later Banthine and tincture of belladonna, 0.4 cc., clearly appeared to be more effective than tincture of belladonna, 0.6 cc. Thereafter Banthine caused, on the whole, a greater decline in activity than tincture of belladonna in either dosage, although throughout the 90-to-240-minute post-medication period the difference between the action of the two drugs was not striking. When the changes

in total contractions following placebo administration were compared with the changes in the drug tests it could be seen that, with the exception of the 150- and 210-minute periods, Banthine, starting with the thirty-minute post-medication interval, caused a greater decline in activity than did the placebos. The differences between the Banthine effect and that noted after placebo administration were most marked beginning with the thirty-minute and continuing through the 105-minute post-medication period. The individual variation in activity is shown by the scattergram for the sixty-to-seventy-five-minute post-medication period. The range in variation was about the same for the Banthine and tincture of belladonna in both dosages and less for the placebos.

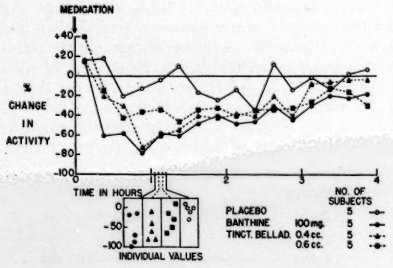


FIGURE 4. *Effect of Banthine, Tincture of Belladonna and Placebos on Total Contractions in Group I Subjects.*

The figure shows that oral Banthine and tincture of belladonna caused a more striking decrease in total contractions (propulsive and nonpropulsive) than was noted after placebo administration during most of the fifteen-minute intervals up to the three-hour post-medication period. Thereafter the differences among the three agents were less marked. The most rapid action was noted with Banthine, which was generally slightly more effective than tincture of belladonna in the dosage of 0.4 or 0.6 cc. The mean values of the changes in activity for each fifteen-minute post-medication period were determined in the same manner as indicated in Figures 2 and 3. The values for Banthine are shown by the black dots, those for belladonna, 0.4 cc., by the triangles, those for tincture of belladonna, 0.6 cc., by the squares and those for the placebo tests by the open circles. The range of the individual variation during the sixty-to-seventy-five-minute post-medication period is shown by the scattergram. Total contractions were measured for five minutes previous to each fifteen-minute period in each test and were expressed in square centimeters of surface area.

Starting with the thirty-minute post-medication period, the percentage decrease in total contractions after placebo administration averaged 17 per cent, whereas in the case of the two drugs the decline in activity averaged 72 per cent for Banthine and 60 per cent for tincture of Belladonna, 0.4 cc. The individual variation in the percentage decrease in total contractions at the sixty-to-seventy-five-minute postmedication period was nearly the same for the two drugs. The range in variation for Banthine was from −15 to −95 per cent; that for tincture of belladonna was −32 to −95 per cent. On the other hand, the range for the individual variation in total contractions after placebo administration for this period was from +35 to −85 per cent.

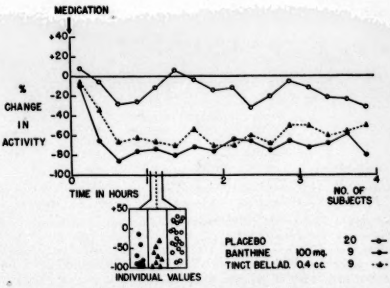


FIGURE 5. *Effect of Banthine, Tincture of Belladonna and Placebos on Total Contractions in Group II Subjects.*

The figure shows that Banthine acted somewhat more rapidly and was on the whole consistently more effective in decreasing total contractions than was the administration of tincture of belladonna, 0.4 cc. Both drugs produced a much more striking effect than was noted after the administration of placebos. The range of the individual variation for the sixty-to-seventy-five-minute post-medication period is shown by the scattergram. The symbols indicating the agents used and the method of the measurement and determination of the percentage changes in activity for each fifteen-minute period were the same as described in Figure 4. The number of subjects included in each drug study at the end of each sixty-minute post-medication period was as follows: at 60 minutes, Banthine 9, belladonna 8, placebos 20; at 120 minutes, Banthine 9, belladonna 7, placebos 19; at 180 minutes, Banthine 7, belladonna 6, placebos 13; at 240 minutes, Banthine 3, belladonna 5, placebos 7.

Group II subjects. Figure 5 shows that at the thirty-minute post-medication period Banthine was almost twice as effective as tincture of belladonna, 0.4 cc. Thereafter the difference between the two drugs was less. With the exception of the 135-minute and 225-minute periods, Banthine remained consistently more effective than did tincture of belladonna, 0.4 cc. As compared to the changes noted after placebo administration, the two drugs caused a much greater decrease in total contractions.

Tone

Group I subjects. In Group I subjects, no marked changes in tone were noted except during the last forty-five minutes of the post-medication period (Fig. 6). At that time tone was consistently increased after the administration of the placebos and tincture of belladonna in both dosages, whereas the tone changes with Banthine ranged from +7 to −7 per cent for that interval. Prior to this period the changes in tone for Banthine averaged −5 per cent; for tincture of belladonna, 0.4 cc., −1

per cent; for tincture of belladonna, 0.6 cc., +6 per cent; and for the placebos, +5 per cent. The range of the individual variation at the sixty-to-seventy-five-minute post-medication period was about the same for tincture of belladonna, 0.4 and 0.6 cc., and placebos and only slightly more for Banthine.

When tone was measured with a centimeter ruler for each five-minute interval throughout the observation period, Table I shows that the comparative changes in tone after the administration of the agents followed about the same trend as that noted with the polar planimeter measurements of surface-area changes presented in Figure 6. After Banthine administration tone remained slightly but consistently decreased throughout the four-hour post-medication interval. In the case of the tests with tincture of belladonna, 0.4 cc., tone was decreased

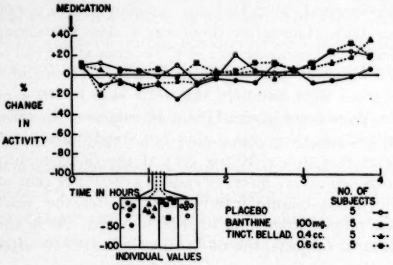


FIGURE 6. *The Effect of Banthine, Tincture of Belladonna and Placebos on Tone in Group I Subjects.*

The figure shows that tone was either unchanged, slightly increased or slightly decreased after the administration of the three agents. On the whole, Banthine caused a slightly greater diminution in tone than was noted after the administration of belladonna or placebos. The range of the individual variation for the post-medication period of sixty to seventy-five minutes is shown by the scattergram. Tone was measured for five minutes previous to each fifteen-minute interval and was expressed in square centimeters of surface area. The black dots (Banthine values), the black squares (belladonna, 0.6 cc., values), the black triangles (belladonna, 0.4 cc.) and the open dots (placebo values) indicate the mean of the sum of the percentage changes in activity for each fifteen-minute period as compared to the last forty-five minutes of the control period.

about the same degree as with Banthine during the sixty-to-ninety-minute post-medication period. Thereafter the decrease in tone was less in the studies with tincture of belladonna, 0.4 cc. In contrast, tone was, with the exception of the ninety-minute post-medication period, slightly but consistently increased after the administration of tincture of belladonna, 0.6 cc. These last values were comparable to the results following placebo administration.

Group II subjects. The studies in Group II subjects showed a definite and consistent decrease in tone after the administration of Banthine and tincture of belladonna, 0.4 cc., the effect being consistently more marked with Banthine than with tincture of belladonna (Fig. 7). Starting with the thirty-minute post-medication period, the decrease in tone for Banthine averaged 27 per cent for the entire period of observation; for tincture of belladonna, 0.4 cc., 14 per cent; and for placebos, +9 per cent. After the administration of placebos, tone was essentially unchanged until the 195-min-

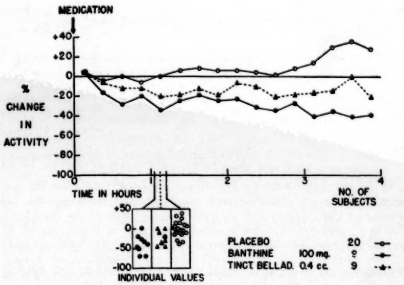


FIGURE 7. *The Effect of Banthine, Tincture of Belladonna and Placebos on Tone in Group II Subjects.*

The figure shows that both Banthine, 100 mg., and tincture of belladonna, 0.4 cc., caused a consistent diminution of tone, the action being somewhat greater with the former than with the latter drug. Tone was essentially unchanged for the first three hours after the administration of placebos; during the remaining hour of the post-medication period tone increased about 20 per cent. The range of individual variations in tone is shown by the scattergram for the post-medication period of sixty to seventy-five minutes. The symbols indicating the agents used and the method of measurement and determination of the percentage variations for each fifteen-minute period were the same as described in Figure 6. The number of subjects included in each drug study at the end of each sixty-minute post-medication period was as follows: at 60 minutes, Banthine 9, belladonna 8, placebos 20; at 120 minutes, Banthine 9, belladonna 7, placebos 19; at 180 minutes, Banthine 7, belladonna 6, placebos 13; at 240 minutes, Banthine 3, belladonna 5, placebos 7.

ute post-medication interval, when it was increased and remained definitely elevated for the remainder of the period of study. As shown by the scattergram, the individual variation was less for tincture of belladonna, 0.4 cc., than for Banthine and for the placebos. The range of variation for Banthine was from +5 to −70 per cent; for tincture of belladonna, 0.4 cc., −3 to −50 per cent; and for the placebos, +40 to −40 per cent.

As shown in Table 1, the changes in tone measured by the centimeter ruler were similar to those shown for the polar planimeter measurements (Fig. 7). Beginning with the thirty-minute post-medication interval, tone was consistently decreased after Banthine administration. The range of the decrease n tone was from 7 to 38 per cent. During this same

interval, tincture of belladonna caused a consistent but smaller decline in tone, the values ranging from −3 to −19 per cent. In contrast, tone following placebo administration changed, on the whole, very little until the 180-minute post-medication period. From this time until the end of the period of study, tone was consistently elevated until the 240-minute period, when it decreased 24 per cent.

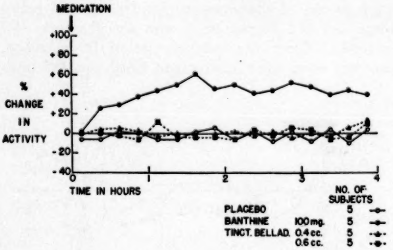


FIGURE 8. *The Effect of Banthine, Tincture of Belladonna and Placebos on Heart Rate in Group I Subjects.*

The figure shows little or no change in heart rate after the administration of placebos and tincture of belladonna in the dosage of 0.4 cc. and 0.6 cc. The administration of Banthine, 100 mg., was followed by a steady increase in heart rate of 25 per cent from the thirty-minute post-medication period to a 62 per cent increase at the 105-minute post-medication period. Thereafter the heart rate slowly decreased to + 40 per cent at the 240-minute post-medication period.

Side-Reactions

In the Group I subjects, changes in heart rate, blood pressure, symptoms, — including dryness of the mouth, — and pupillary size were noted before and after drug and placebo administration. In Group II subjects these data are confined to the changes in heart rate before and after the administration of Banthine in nine tests, and placebos in six tests.

Heart rate. As shown in Figure 8, the changes in heart rate after the administration of tincture of belladonna, 0.4 cc. and 0.6 cc., and placebos were minimal. Except for a 14 per cent increase in heart rate following the administration of tincture of belladonna, 0.6 cc., at the seventy-five-minute post-medication period and an 11 per cent increase in heart rate at the 240-minute period following the administration of tincture of belladonna, 0.4 cc., the values for the tests with the placebos and tincture of belladonna in both dosages varied within +10 and −10 per cent. On the other hand, starting at the thirty-minute post-medication interval, there was a +24 per cent increase in the heart rate after the administration of Banthine. This steadily increased until the seventy-five-minute post-medication interval, when the rate was increased to a +60 per cent. Thereafter there was a slow fluctuating decline in heart rate to a +40 per cent at the end of the four-hour post-medication period. Comparable changes were noted in the heart rate in the nine Banthine tests in the Group II subjects. In these individuals there was a slow but steady increase in heart rate to a +10 per cent at the thirty-minute post-medication interval and to a +50 per cent at the ninety-minute interval. Thereafter the heart rate ranged from +40 to +60 per cent. As in the Group I subjects, the fluctuation in heart rate after the placebo administration varied well within +6 and −6 per cent.

The effect of the change in posture on heart rate at the end of the test period was observed in both Group I and Group II subjects. Although the heart rate increased after Banthine administration to about 150 per minute in 3 subjects, the percentage

TABLE 1. *Data on Tone After the Administration of Banthine, Tincture of Belladonna and Placebos.**

Interval After Medication	Group I Subjects† Change After Banthine (100 mg.)	Change After Belladonna (0.4 cc.)	Change After Belladonna (0.6 cc.)	Change After Placebos
min.	%	%	%	%
15	−10	+ 7	+25	+10
30	−12	− 4	+ 4	+10
45	−14	− 8	+ 3	+11
60	−15	−14	+ 2	+ 4
75	−18	−15	+ 5	+ 3
90	−13	−14	−11	+ 3
105	−18	− 9	+ 3	+ 7
120	− 5	− 3	+ 3	− 1
135	−11	− 2	+ 2	− 7
150	−13	− 3	+18	+ 8
165	−12	− 4	+ 7	+ 6
180	− 8	− 5	+ 7	+10
195	−14	+ 5	+11	+ 4
210	−16	+ 7	+12	+ 4
225	− 8	+ 4	+18	+20
240	− 6	+ 8	+19	+24

*In each test, the average value for each fifteen-minute period was divided by the average value for the last forty-five minutes of the control period. The mean percentage change for any one group of tests was then obtained by dividing the mean of the sum of the values per fifteen-minute period by the number of tests in that period.

†All 5 subjects in Group I were studied for the duration of the four-hour post-medication period.

increases in heart rate associated with changing from the lying to the standing position were no different from those noted in the placebo and tincture-of-belladonna tests.

Blood pressure. Blood pressure was found to vary only slightly after the administration of the three agents. When the range of systolic blood-pressure values during the control period was compared to these values taken during the post-medication period in Group I subjects, a small increase in the upper limit of this range in systolic pressure was noted in all except one test. This increase varied from 4 to 12 points. During the post-medication period the upper limit of the range of diastolic blood-pressure values was increased from 9 to 18 points in six tests, was unchanged or increased up to 8 points in twelve tests and was decreased 8 points in one test and was increased 40 points in another. The lower limit of the range of systolic blood pressure following the administration of the agents varied from +10 to −10 points in 17 tests, was increased from 11 to 14 points in two tests and decreased 34 points in one test. The lower limit of the range of diastolic pressure after the administration of the agents varied from +6 to −6 per cent in 16 tests and up to +10 to −12 per cent in four tests. The changes in blood pressure bore no consistent relation to the particular agent given or the time interval following its administration.

Dryness of the mouth. In Group I subjects 1 man (Subject 1) showed a slight increase in dryness of the mouth after the administration of the placebo, with Subjects 2, 3 and 5 (Table II) showing no distinct change: in Subject 4 the findings were inconclusive because of incomplete data. After the administration of tincture of belladonna, 0.4 cc., 4 subjects (1, 3, 4 and 5) noted a slight to moderate increase of dryness of the mouth, with one subject, No. 2, noticing little or no change. After the administration of tincture of belladonna, 0.6 cc., 3 subjects (1, 2 and 5) reported a moderate increase in dryness of the mouth, whereas 2 subjects (3 and 4) noted a slight increase. On the other hand, after Banthine, 100 mg., was administered, 2 subjects (4 and 5) noticed a marked increase in dryness of the mouth. Subjects 1 and 3 noted a moderate increase; in Subject 2 there was only a slight increase. It was concluded from these five tests that dryness of the mouth was more striking after the administration of Banthine than after the use of tincture of belladonna in dosages of either 0.4 cc. or 0.6 cc. Changes in dryness of the mouth were minimal after placebo administration.

Pupillary size. In 1 of the 5 subjects in Group I, measurements were not made of pupillary size after the administration of the placebo or of Banthine. No changes in the size of the pupils were noted after the administration of placebos or of tincture of belladonna, 0.4 cc. In the tests with tincture of belladonna, 0.6 cc., only 1 subject showed a slight increase after administration of the drug. In the Banthine test 1 subject showed a slight increase in pupil size; in the other 3 there was no change. We concluded, therefore, that changes in pupillary size represented a minimal side-effect in these tests.

TABLE 1 (*Concluded*).*

Interval after Medication	Group II Subjects: After Banthine (100 mg.) Change	After Banthine (100 mg.) No. of tests	After Belladonna (0.4 cc.) Change	After Belladonna (0.4 cc.) No. of tests	After Placebos Change	After Placebos No. of tests
min.	%		%		%	
15	+22	9	+ 3	9	+ 1	20
30	− 7	9	− 3	9	+ 1	20
45	−25	9	− 9	9	− 4	20
60	−22	9	−13	8	− 5	20
75	−28	9	− 7	8	− 7	20
90	−26	9	−11	8	+ 3	20
105	−17	9	−15	7	+10	20
120	−21	9	−13	7	− 4	19
135	−26	9	−11	7	+ 3	18
150	−29	9	−16	6	− 1	17
165	−25	8	−15	6	+ 2	16
180	−27	7	−18	6	+10	13
195	−32	7	−14	6	+11	12
210	−38	6	− 9	6	+24	10
225	−31	5	−18	5	+28	10
240	−35	3	−19	4	−24	9

Discussion

Data have been presented showing the comparative changes in motility of the upper small intestine in man following the oral administration of Ban-

thine, 100 mg., tincture of belladonna, 0.4 cc. and 0.6 cc., and placebos. The results present objective evidence in healthy adult subjects that under these experimental conditions Banthine caused a pronounced decrease in both propulsive contractions and total contractions (propulsive and nonpropulsive). This effect was evident at the thirty-minute post-medication period and usually became maximal fifteen minutes later. Thereafter, either this maximal effect was maintained or the action of the drug decreased slightly with the passage of time. The only exception was noted for total contractions in Group I subjects. Beginning with the 105-minute post-medication period, there was a steady recovery of total contractions up to the end of the study, when these contractions were decreased only 30 per cent. Banthine acted more rapidly than did tincture of belladonna in dosages of 0.4 cc. or 0.6 cc. Beginning with the sixty-minute post-medication period, Banthine was, on the whole, slightly more active than tincture of belladonna in either dosage. In Group I subjects there was little difference in the effect on propulsive contractions of tincture of belladonna in either dosage until the beginning of the 150-minute post-medication interval. At this time, and for the remainder of the observation period, tincture of belladonna, 0.4 cc., diminished propulsive contractions only slightly more than was noted after placebo administration. On the other hand, we were surprised to find that tincture of belladonna, in the smaller dosage of 0.4 cc., caused an appreciably greater decline in total contractions than did tincture of belladonna, 0.6 cc., at the sixty- and seventy-five-minute post-medication period and a slightly greater decrease during the next forty-five minutes. Our failure to show a significant difference between the action of tincture of belladonna in a dosage of 0.4 cc. as compared to one of 0.6 cc. may be due to the fact that the method of recording motor activity is not sufficiently sensitive to bring out minor changes in such movements.* It may also be due to the fact that changes in motility do not vary proportionately with changes in dosage.

The effect of Banthine on tone was less marked than its effect on contractions. Figures 6 and 7 and Table 1 show that although this decline in tone was small it was somewhat greater than that noted after the administration of tincture of belladonna.†

TABLE 2. *Degree of Dryness of Mouth* Before and After the Administration of Banthine, 100 Mg., Belladonna, 0.4 cc. and 0.6 cc., and Placebos.*

DRUG	SUBJECT NO.	GROUP I SUBJECTS																		
		TIME *minutes*																		
		45	30	15	0	15	30	45	1 hr.	15	30	45	2 hr.	15	30	45	3 hr.	15	30	45	4 hr.
Banthine	1	1	1	1		1	1	2	2	2	3	2	3	3	3	3	3	3	3	3	3
	2	2	2	2		1	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3
	3	0	1	0		1	1	1	1	2	3	3	2	2	2	2	1	1	1	1	1
	4	—	0	—		—	—	—	—	—	3	4	4	3	2	2	2	—	—	1	—
	5	0	0	1		1	1	1	1	2	3	4	4	4	4	4	4	4	4	4	4
Belladonna, 0.4 cc.	1	2	3	3		4	4	4	4	4	4	4	4	—	4	—	4	—	4	—	4
	2	0	0	0		0	0	0	0	0	0	0	0	—	0	—	1	—	1	—	0
	3	0	0	0		0	0	1	1	2	2	2	2	1	—	1	—	2	—	1	1
	4	0	1	0		0	0	0	1	1	1	1	1	1	—	1	—	1	—	1	—
	5	1	1	1		3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4
Belladonna, 0.6 cc.	1	0	0	0		0	0	0	1	2	1	1	2	2	2	3	3	3	3	3	3
	2	2	2	1		1	1	1	1	1	1	2	3	3	2	1	1	2	2	2	2
	3	0	1	0		0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1
	4	0	0	0		0	0	0	1	2	1	1	1	3	1	1	1	0	0	0	0
	5	1	1	1		0	1	1	2	2	2	2	3	3	3	3	3	3	3	3	3
Placebo	1	1	1	1		1	2	2	2	—	2	—	2	—	2	—	2	—	2	—	3
	2	0	0	0		0	0	0	0	0	0	0	0	—	1	—	2	—	3	—	1
	3	—	0	—		0	0	1	2	0	0	0	1	—	1	—	1	—	1	—	1
	4	—	0	—		—	—	1	—	—	—	1	—	0	—	—	—	—	—	—	—
	5	0	0	1		1	1	2	2	1	1	1	1	1	1	1	1	1	0	1	2

*0 = no dryness; 1 = slight dryness; 2 = moderate dryness; 3 = marked dryness; 4 = very marked dryness.

We have no explanation for the finding that tincture of belladonna, 0.4 cc., had more effect on tone than in the larger dosage of 0.6 cc. These findings of the inhibitory action of Banthine on intestinal motility are in agreement with our preliminary observations and those of previous workers.[3, 6, 12]

The side-effects noted in these studies were negligible except for an increase in heart rate following Banthine administration and dryness of the mouth observed after the administration of both Banthine and tincture of belladonna. The maximal elevation of heart rate following Banthine administration occurred at the sixty-to-ninety-minute post-medication period. This effect persisted for the duration of the tests. We believe that under the experimental conditions of these studies the changes in heart

*The statistical significance of the effect of the drugs and placebos on propulsive and total contractions was determined for the sixty-to-seventy-five-minute post-medication period for the data in Figures 2 through 5. All significances were based on $P. = 0.05$. Banthine and tincture of belladonna in dosages of 0.4 cc. and 0.6 cc. caused a significantly greater decline in activity than did the placebos. None of the differences between Banthine and tincture of belladonna in either dosage or between the two dosages of tincture of belladonna were significant.

†With significances based on $P. = 0.05$, it was found for the data in Figure 6 at the sixty-to-seventy-five-minute post-medication period that the effect of the drugs on tone was not significantly different from that of the placebos or from each other. For the data on the sixty-to-seventy-five-minute post-medication period in Figure 7, Banthine and tincture of belladonna produced a significantly greater decline in tone than did the placebos, but there was no significant difference between the effects of the two drugs.

rate represent an inhibitory effect of the vagal stimuli on heart action. Elevation of heart rate was either minimal or absent in the tincture-of-belladonna or placebo tests. This action of Banthine appears to be of no clinical significance, for, so far as we are aware, elevation of heart rate has been observed only occasionally in patients receiving Banthine continuously during treatment.

This inhibitory effect of Banthine on motility can readily explain the rapid relief of pain or discomfort reported by patients receiving the drug therapeutically for peptic ulcer. Its action takes place more rapidly and is more marked and sustained than that of tincture of belladonna in therapeutic dosages. Unfortunately, the decline in motor activity following the administration of this new drug has not been achieved without occasionally producing side-reactions comparable to, or more pronounced than, those seen with the belladonna alkaloids. It appears, however, with the prolonged use of Banthine, that unpleasant side-effects become less and less pronounced.[7] Whether Banthine is a superior drug for the treatment of peptic ulcer or other disorders of the gastrointestinal tract must await clinical trial in such patients. Because of the many factors that influence these disorders and the spontaneous variability of their course, we think that such a clinical study should include several years of observation in which the treatment remains, so far as possible, unchanged except for the alternate use of Banthine, the belladonna alkaloids and placebos.

Summary

The comparative action of the oral administration of Banthine, 100 mg., tincture of belladonna in dosages of 0.4 and 0.6 cc. and placebos on the motility of the upper small intestine has been studied in 31 healthy adult subjects. The changes in propulsion, total contractions (propulsive and nonpropulsive) and tone were determined by a multiple-balloon-kymograph recording method.

Banthine was found to cause a striking decrease in propulsive and total contractions and a slight to moderate decrease in tone. Banthine acted more rapidly and inhibited motility to a greater degree than did tincture of belladonna in either dosage. Both drugs produced significantly greater effects than were observed after placebo administration. Dryness of the mouth was more noticeable with Banthine than with tincture of belladonna. Banthine administration was followed by an increase in heart rate, which was not observed in the tincture-of-belladonna tests.

Although Banthine compares very favorably with tincture of belladonna in its inhibitory action on intestinal motility, it remains for long-term clinical studies to determine which agent is of greater therapeutic value in the sustained treatment of gastrointestinal disorders.

We wish to acknowledge the technical assistance of Mr. Thomas Fazio, Miss F. Jean Emery and Miss Marcia Black and to thank Dr. L. D. Calvin, Biological Research Division, Research Department, G. D. Searle & Company, Chicago, for the statistical calculations.

References

1. Hambourger, W. E., Cook, D. L., Winbury, M. M., and Freese, H. B. Pharmacology of β-diethylaminoethyl xanthine-9-carboxylate methobromide (Banthine) and chloride. *J. Pharmacol. & Exper. Therap.* **99**:245-254, 1950.
2. Longino, F. H., Grimson, K. S., Chittum, J. R., and Metcalf, B. H. Orally effective quaternary amine, Banthine, capable of reducing gastric motility and secretions. *Gastroenterology* **14**:301, 1950.
3. Kern, F., Jr., Almy, T. P., and Stolk, N. J. Effects of certain antispasmodic drugs on intact human colon, with special reference to Banthine (β-diethylaminoethyl xanthine-9-carboxylate methobromide). *Am. J. Med.* **21**:67-74, 1951.
4. Smith, C. A., Woodward, E. R., Janes, C. W., and Dragstedt, L. R. Effect of Banthine on gastric secretion in man and experimental animals. *Gastroenterology* **15**:718-726, 1950.
5. Grimson, K. S., Lyons, C. K., and Reeves, R. J. Clinical trial of Banthine in 100 patients with peptic ulcer. *J. A. M. A.* **143**:873-877, 1950.
6. McHardy, G., Brown, D. C., Marek, F., McHardy, R., and Gaddy, J. H. Banthine — clinical evaluation in gastroenterology. *J. A. M. A.* (in press).
7. Ellis, D. C., Chapman, W. P., and Jones, C. M. Personal communication.
8. Lepore, M. J., Golden, R., and Flood, C. A. Oral Banthine, effective depressor of gastrointestinal motility. *Gastroenterology* **17**:551-559, 1951.
9. Abbot, F., and Wolf, S. Effects of Banthine on gastric function of normal man and subjects with peptic ulcer. *Gastroenterology* (in press).
10. Chapman, W. P., and Palazzo, W. L. Multiple-balloon-kymograph recording of intestinal motility in man with observations on correlation of tracing patterns with barium movements. *J. Clin. Investigation* **28**:1517-1525, 1949.
11. Chapman, W. P., Rowlands, E. N., and Jones, C. M. Multiple-balloon-kymographic recording of comparative action of oral administration of atropine, tincture of belladonna and placebos on motility of upper small intestine in man. *New Eng. J. Med.* **243**:1-8, 1950.
12. Chapman, W. P., French, A. B., and Hoffman, P. S. Multiple-balloon-kymographic recordings of comparative action of Banthine (ethyl dimethyl Beta-9-xanthine carboxylate ethyl ammonium chloride), placebos, and tincture of belladonna on motility of upper small intestine in man. *J. Clin. Investigation* **29**:803, 1950. (Abstr.)

ARROW WOUNDS*

J. A. Lundy, M.D.†

WORCESTER, MASSACHUSETTS

THIS day and this place, our new Medical Library Hall, are the time and place to remind you of the long tradition behind the Annual Oration of the Worcester District Medical Society.

The first oration of which we have record was given one hundred and fifty-six years ago. Since 1795 an oration has been given annually to this society almost without interruption to the present day. There were, however, a few calm years with no orations. For instance, a hundred years ago the orator declined to give his oration and was excused. It makes one realize that if one has nothing to say it is better to decline, as Dr. Marshall did in 1851. Of course this is a different, more voluble age. As we read the papers and periodicals, listen to the politicians and watch television in 1951, we realize that nowadays even if one has nothing to say he nevertheless says it.

It is interesting that forty-three years ago the orator discussed vivisection — and his paper was so good that there is little to add to it today. It is even more interesting that the opponents of vivisection are still using the same arguments and methods he describes — and with the same success.

In these orations are also described diseases and problems now extinct by virtue of new methods and discoveries. However, in many old pages there are items about forgotten diseases, principles and truths that have lain in the dust so long that they are considered new discoveries when later brought to light.

It is only recently that the disease of one of our members, a former orator and son of an orator in this society, remained undiagnosed at a large medical center until an old visiting practitioner identified it as a condition no longer described in our textbooks. Although the literature was full of the subject fifty years ago, subsequent articles and textbooks had ignored the disease.

This is true also of my present subject — "Arrow Wounds." Nothing has been written recently about arrow wounds. In fact, very little has ever been written about them. Although there are few Indians left who can shoot an arrow we do have modern devotees of archery as a sport. So my subject is not entirely academic.

It may excite curiosity that an internist should choose a surgical subject for his oration. There is adequate explanation: When arrow wounds were prevalent a physician was a physician, and he treated the arrow wounds of his day. Although there were surgeons then, internists did not yet exist as such. This internist is confident that of the many distinguished surgeons in our midst few if any are as well read as he on the subject of arrow wounds.

Arrow wounds may be actual and figurative. Because the literal aspect of this subject is the more interesting, the first part of this paper will be devoted to real arrow wounds.

Etiologic agent. An arrow. This is a missile composed of a head, a shaft and a feathered end.

Pathology. A penetrating wound in whatever part of the anatomy is struck.

Diagnosis. The feathered end of the shaft of an arrow protruding from the subject usually indicates the diagnosis.

Complications. In this country sepsis was the most common complication, taking the form of abscesses, empyema, peritonitis or tetanus. In Africa and South America, where poisoned arrows are still used, the toxicity of the poison is the most important complication.

Treatment. All authorities agree that one should never try to extract an arrow by pulling on its shaft — first, because of the shape of the head, which does not favor withdrawal, and secondly, because the thongs fastening the head to the shaft tend to loosen inside the body and thirdly, because the shaft is the best guide to the position of the head to be recovered. If the shaft has penetrated to the opposite side of the body and the head can be felt there, a counter incision is made. The head is then removed from the shaft and the shaft withdrawn. This maneuver was later rediscovered and applied to the removal of fishhooks. It is described by Christopher in his *Minor Surgery*. Most rural practitioners know that one doesn't pull out a fish hook by its shaft but that it is best to drive the fishhook in more deeply or make a counter incision to present the point, clip off the barb and then pull out the shaft.

In the old days extensive surgical search for an arrowhead imbedded deeper than 2½ inches was not often carried out, and the arrowhead was left *in situ*, causing suppuration and death; today our surgeons would never turn back from such an exciting search. The treatment of sepsis, as we know, has changed for the better. But the old principle "Where there is pus, evacuate it" still holds, however often it is ignored.

The principle *ubi pus ubi evacua* is almost due for a rediscovery. As internists we find the signs of localized sepsis masked by antibiotics or ignored

*Annual Oration of the Worcester District Medical Society, given on December 12, 1951.

†Senior physician, Worcester City Hospital; physician and cardiologist, Hahnemann Hospital, Worcester; assistant physician, St. Vincent Hospital, Worcester.

by those who grew up in the antibiotic age. This ignorance often prolongs the illness of the patient, obscures the diagnosis and sometimes contributes to death. A whole paper could be devoted to the forgotten fundamental principles of surgery and medicine. Some of them need to be rediscovered.

No medical paper of this day and age is considered worth its salt unless some statistics and one or two cases histories are included. To follow the fashion, I submit the following statistics, cited by J. H. Bill in the *American Journal of Medical Sciences* of October, 1862.

Dr. Bill compiled these statistics from many sources other than his own experience. They have been quoted only once before — in Hamilton's *Treatise on Military Surgery*, published at about the time of the Civil War.

Arrow wounds of upper extremities	28	1 death
Lower extremities	6	1 death
Head superficial	2	
Head penetrating	3	2 deaths
Spinal marrow	1	1 death
Chest superficial	9	
Chest penetrating lung	6	4 deaths
Chest penetrating heart	2	2 deaths
Abdomen superficial	6	3 deaths
Abdomen, intestine wounded	15	15 deaths

The arms and abdomen were the areas most frequently wounded. This preponderance of arm wounds was explained by the facts that anyone who saw an arrow coming instinctively tried to ward it off and that the Indians aimed for the abdomen because they knew that such wounds were usually fatal.

Arrow wounds penetrating the skull would nowadays require an emergency call for a neurosurgeon. Dr. Bill, however, submits his treatment in the following case:

Case Reports

Case 1. "Miguel Nigro, the post guide at Fort Union, was shot with an arrow by a Utah Indian. I found the arrow head sticking in the left parietal bone, the shaft having been detached. I made traction on it and drew it out of the wound. The symptoms of compression present at once vanished, the man turned over and sneezed, and rose upon his feet. I had made arrangements to trephine the skull if necessary, but I had probably restored to its proper level that portion of the inner table which was depressed, so that measure was unnecessary. The cause of the depression was gone, and I had nothing to trephine for. The next day the man complained of headache .... His face was flushed, eyes suffused, pulse hard and irregular. I ordered croton oil, shaved his head, and applied cold. Presently, when delirium came on, I bled him until he fainted. This bleeding was repeated the night of the same day. The next day he was greatly better. The croton oil had operated well. The man was left to recover; which he did in three weeks."

This case was attended by Dr. C. A. Pope, professor of surgery, St. Louis Medical College, Missouri.

Case 2. "A lieutenant in 1860 in a skirmish with Indians in New Mexico received an arrow shot in the left superior maxilla. The spear shaped iron point, two and three quarter inches long, with a small neck for the fastening of the shaft of the arrow by means of the sinews of a deer, entered the face a little below the orbit and was completely imbedded in the bone. Its direction was backwards and outwards. The surgeon of the post immediately endeavored to extract the foreign body. At first it was hoped that this might be accomplished by forcible traction on the arrow itself. The only effect of this, however, was to detach the feathered wooden shaft from the iron headed point, which remained firmly in the bone.

[You see, he violated the first principle — never to make traction on the shaft.]

"Various means were used in an attempt to extract the head but all failed. Slight secondary hemorrhage occurred from the nose off and on for the next few weeks. I saw him five weeks after the injury at his home in St. Louis. There was some enlargement of the left side of the face. The wound of the cheek had skinned over. A muco-purulent discharge issued from the corresponding nostril. I felt a hard point beneath the integuments of the cheek and incising the scar found the neck of the arrow head. I failed in its extraction until I used a pair of powerful forceps. A smart hemorrhage from the nostril and wound followed. Rest, opium, cold, plugging and bandage arrested the hemorrhage. A few slight hemorrhages subsequently occurred.

"The case now seemed to progress favorably and he was able to go out on the streets. On a visit to my office he complained of a stiffness and inability to separate the jaws as widely as usual. I advised him to make gentle efforts to open the mouth. In less than an hour from this time his trouble commenced.

"The whole cheek became hot and painful. High fever with renewed hemorrhage set in and caused me much anxiety. Extensive extravasations of blood took place, and to relieve the tension, I made free incisions both in the mouth and on the cheek and neck from which large clots were pressed out. The hemorrhage continuing at intervals, and finally on three successive nights occurring with regularity about twelve o'clock, and the patient being reduced to the lowest point of safety, I determined to tie the carotid without delay.

"This was done by candle light on the night of the 16th of December two months after the receipt of the injury. Such was the extreme condition of the patient he fainted during the operation, although he was in the recumbent position. The operation itself was a delicate and difficult one, as the parts were very much swollen and altered in their relations by infiltrations. The bleeding never recurred, and the final recovery of the patient was complete."

This lieutenant lived to fight again; years later he was killed in the Battle of Fredericksburg. He was General Bayard.

If one cannot infer honesty, faithfulness, skill, knowledge and the attributes of a real physician from this account, the subject of arrow wounds had better not have been revived.

Arrow wounds have been inadequately discussed. A revival such as this one is only an introduction to the old literature; in such old volumes one finds odd treasures of knowledge, humor and truth and is often fascinated, enlightened and amused.

The problem of "How to Choose a Nurse" is discussed in an old book in our Medical Library. What subject is more timely? However, this book dwells mostly on certain feminine anatomic prerequisites of nursing that are today much publicized in fashion and on television — because, of course, it is a book on wet nurses.

The volume that contains the article on arrow wounds also has an excellent discussion of cardiac murmurs by Austin Flint. Much of the enjoyment of pursuing a subject down through the years is the discovery of adjacent articles and volumes long undisturbed. In the same volume that binds Dr. Bill's article on arrow wounds, a Dr. Salisbury of Ohio records his investigation of fungi in the modification of disease, and another author discusses

cholesterol and liver function. Could more timely publications than these be found in our own literature, ninety years later?

Unlike the riflemen of today, our archers rarely wound their neighbor; hence, to bring our subject up to date arrow wounds must be discussed in a figurative sense.

We, the medical profession, are the wounded. The arrows stick out all over us. The wounds are the result of barbed attacks made by persons and groups both inside and outside the profession. Some wounds have been self-inflicted.

We are the recipients of arrows shot from propaganda machines of pressure groups. We are shot at by disgruntled or rebuffed patients who now find us vulnerable. Barbed remarks issue from some of our colleagues.

These have long been lethal weapons. The sharp barb, the short, silent flight of the arrow from its concealed origin, and the ancient trick of placing on the shaft pretty feathers of adornment and direction are still used in modern times.

One no longer destroys by honest, direct attack. He destroys by indirection, slow attrition and attacks from within. We are the attacked. The world-wide trend toward socialization, however well intentioned, in this country has been expedited not by honest evaluation but by destruction, innuendo and propaganda. It has been helped by the money and platform privileges of appointed officials. It has been conveniently ignored by elected officials. These facts are obvious, and they are matters of record. The wounds of officialdom are well documented.

The defense against these arrows has been hastily raised by our own organization, the American Medical Association. The silent flurry of arrows in our direction has wounded the district societies less, because we are not only individuals but also a group. And through our group efforts these flaming-arrow attacks have been modified. We owe great admiration to the American Medical Association, although in conceding it we admire ourselves, because we are the American Medical Association. The officers are our representatives, voicing our majority opinion. They are making mistakes, just as we would make them, but they are achieving successes that we would never achieve alone.

What is not quite so obvious is our own individual susceptibility to the arrow wounds of neighborhood gossip. I do not believe that we as individuals have prevented these wounds as well as we have done as a group.

We are wounded as a group by the proponents of a new social order who are working to gain their ends. We are wounded as individuals by any of our neighbors who think that they have not received adequate service, understanding or sympathy.

Every patient who complains about his inability to talk to his physician except during office hours; every patient who is startled by an unexpected fee; and every patient who is rebuffed by any one of us may well go home to manufacture his particular arrow — and he may wait to shoot it until an opportune time presents itself.

What has happened to us? We have been extolled in literature as outstanding members of society. Stevenson's tribute to our profession has been quoted too often to bear repetition here.

I prefer to quote from Hamlet — in no tribute:

> I have shot mine arrow o'er the house
> And hurt my brother

Our arrows have been those of brusqueness, of lack of coverage and of lack of respect. They have hurt our patients, who are our brothers, and they don't like it.

It was much more enjoyable to discuss physical arrow wounds than it is to discuss the figurative arrow wounds of today. In my short time of practice I have seen the change in our status that has come about as a result of these wounds on our collective person. People used to tip their hats to us; they respected us. They expected us to perform miracles without benefit of sulfonamides and penicillin. If we failed they were sure that we had done our best. In my own lifetime this attitude has changed.

We must face the change. We were leaders when J. H. Bill published his treatise on arrow wounds in 1862. We are enfeebled by our wounds as we approach 1952, only ninety years later.

But we do little except lick our wounds and complain. We wish for the giants of the past to lead us. We forget that each physician in the past was a giant and a leader in his community. We decry some of the decisions of our leaders in our district, state and national societies. We forget that we are the society. These men are ourselves, because our organization is a democracy and they reflect us. They, as representatives of a group, can defend us the better — but they rise no higher then do we, the members of the group.

Let us remember the past and face the present. Let us do this as students of medicine pursuing fundamental principles and practices — and let us do it as citizens recalling the idealism and the fortitude of the past to resist the weakness, materialism and socialistic dependency of the present.

THE RECTAL ADMINISTRATION OF AUREOMYCIN IN CHILDREN*

A. C. Siegel, M.D.,† G. H. Nickerson, M.D.,‡ and C. D. Cook, M.D.§

BOSTON

AUREOMYCIN, when given orally, particularly in infants and children, may be difficult to administer, and may occasionally produce nausea and vomiting. Children may be unable to take capsules, and attempts to disguise the bitter taste of the drug with flavoring have not been entirely successful in facilitating its use in the pediatric age group. Such substances as aspirin, barbiturates, glucose and water are effectively absorbed from the rectum; hence, it seemed possible that aureomycin might equally well be absorbed in this fashion. For these reasons, and because rectal administration of the antibiotic had already been adopted by many practitioners, the present investigation of the efficacy of the rectal route was carried out.

Table 1. *Serum Levels of Aureomycin After Single Rectal Dose.*

Patient	Weight	Dose	2-3 Hours after Administration	4-6 Hours after Administration	10-12 Hours after Administration	24 Hours after Administration
	kg.	mg./kg.	microgm./ml.	microgm./ml.	microgm./ml.	microgm./ml.
A. G.	20	25	0.0018	0.25	0.5	0.25
B. L.	34	29	0.15	0.25	0.15	0.06
J. R.	25	20	0.125	0.15	0.15	0
P. B.	15	66	0.25	0.5	0.25	<0.125
W. B.	30	33	0.125	0.25	0.125	0
J. T.	22	23	0	0.125	0	0
J. P.	40	50	0.125	0.625	0.05	0
T. C.	22	34	0.15	0.25	0.125	<0.125
Range			0-0.25	0.125-0.625	0-0.5	0-0.25

Methods

The drug was given to 20 children, ranging in age from four to twelve years, who either were convalescing from acute illnesses or had noninfectious diseases. Initially, aureomycin capsules were either punctured at both ends and inserted into the rectum or emptied into 10 to 15 cc. of water and administered with a bulb syringe. Later aureomycin suppositories‖ were used. The study was divided into two sections.

Eight children received the drug rectally in single doses of 20 to 66 mg. per kg. of body weight. Blood

Table 2. *Serum Levels of Aureomycin After Rectal Administration Every Six Hours.*

Patient	Weight	Dose	No. of Doses Given	3 Hours After Initial Dose	6 Hours After Initial Dose	12 Hours After Initial Dose	18 Hours After Initial Dose	24 Hours After Initial Dose	36 Hours After Initial Dose	48 Hours After Initial Dose	72 Hours After Initial Dose
	kg.	mg./kg.		microgm./ml.	microgm./ml.	microgm./ml.	microgm./ml.	microgm./ml.	microgm./ml.	microgm./ml.	microgm./ml.
L. T.	22	34	3	0.25	0.5	—	—	0.5	0.2	—	—
B. W.	40	38	3	0.05	0.4	0.8	—	1.6	0.4	—	—
J. L.	22	34	3	0.05	0.1	—	—	0.4	<0.05	—	—
B. R.	25	40	3	0.05	—	1.6	—	1.6	0.4	—	—
J. W.	20	25	3	0.1	0.4	0.8	—	0.8	<0.05	—	—
W. F.	22	23	3	0.2	0.5	1.0	—	1.0	0.4	<0.05	—
J. H.	40	25	3	0.05	2.0	2.4	—	0.5	—	<0.05	—
J. V.	25	80	3	0.05	1.6	—	—	1.0	—	0.1	—
L. A.	35	43	8	—	0.4	0.8	1.6	1.6	1.6	1.6	0.4
J. S.	35	29	4	—	0.2	0.4	0.2	0.4	—	0.2	<0.05
R. L.	25	20	4	—	0.2	0.2	<0.2	0.4	0.2	<0.2	<0.05
P. H.	20	25	4	—	0.4	0.8	1.6	0.4	<0.2	—	—

Table 3. *Comparison of Serum and Urine Aureomycin Levels and Total Urine Output Following Rectal Doses Every Six Hours.*

Patient	Weight	Dose	No. of Doses Given	3 Hours After Initial Dose		6 Hours After Initial Dose		9 Hours After Initial Dose		16 Hours After Initial Dose	
				Urine	Blood	Urine	Blood	Urine	Blood	Urine	Blood
	kg.	mg./kg.		microgm./ml.		microgm./ml.		microgm./ml.		microgm./ml.	
J. S.	35	29	4	4	—	4	.2	16	—	16	.4
L. A.	35	43	8	80	—	160	.4	64	—	64	.8
R. L.	25	20	4	32	—	16	.2	4	—	32	.2
P. H.	20	25	4	2	—	2	.4	—	—	4	.8

*From the Department of Pediatrics, Harvard Medical School, and the Division of Clinical Laboratories, Children's Medical Center.

†Junior assistant resident in medicine, Children's Hospital.

‡Formerly, assistant resident, Children's Hospital; associate physician, Alexandra Hospital, Montreal.

§Formerly, chief medical resident, Children's Hospital; instructor in pediatrics, Harvard Medical School.

‖The contents of a capsule were used in a cocoa-butter base and supplied in 500- and 1000-mg. suppositories. These were supplied by the Lederle Laboratories Division of the American Cyanamid Company.

samples were collected at two to three hours, four to six hours, ten to twelve hours and at twenty-four hours.

Twelve children received aureomycin rectally in multiple doses of 20 to 80 mg. per kg. in each dose. Eight of these children were given the drug every six hours for 3 doses. Blood samples were collected at three, six, twelve, twenty-four and forty-eight hours (3 patients) after the first dose. Four patients received aureomycin rectally for longer periods — 3, every six hours for 4 doses, and 1, every six hours for 8 doses. Blood samples were collected from these patients at six, twelve, eighteen, twenty-four, forty-eight and, in 1 patient, sixty hours after the initial dose. In addition, in this latter group of 4 patients urine samples were collected every three hours for a period of forty-eight to seventy-two hours, varying with the number of doses of aureomycin. The urinary excretion of aureomycin was determined at three-hour intervals because it was believed that maximal urine recovery could not be anticipated if the urine were allowed to remain in the bladder for longer periods. Patients whose urinary excretion was being studied were given liberal fluid intakes. All urine and blood samples were placed in the deep-freeze as soon as collected. The specimens were stored from two to four weeks before the time of assay. Both urines and bloods were assayed by the method of Dornbush,[1] using standard cultures of *Bacillus cereus No. 5** in the bioassay.

Results

Serum Levels of Aureomycin after Single Rectal Dose

Table 1 summarizes the levels obtained. These patients received doses of 20 to 66 mg. per kg. The chart does not include 4 patients who expelled the drug within one hour after administration. It will be noted that a maximum level ranging from 0.125 to 0.625 microgm. per ml. of serum was obtained at four to six hours after the administration of this single dose. There was marked inconsistency in the duration of the levels; at ten to twelve hours after administration, values of 0 to 0.5 microgm. per ml. were obtained, and at twenty-four hours values of 0 to 0.25 microgm. per ml. were obtained. This, then, represents a significant variance in levels achieved and a failure to sustain these levels over six hours, as compared to sustained therapeutic levels achieved with a single oral dose of aureomycin.[2] Thus, if aureomycin is given rectally, a lapse of four hours can be expected before even low levels can be obtained. With doses of 20 to 66 mg. per kg., maximum levels of 0.625 microgm. per ml. of serum were obtained, with considerable variance between maximal and minimal doses and with a mean value of 0.27 microgm. per ml. of serum. These values compare unfavorably with the levels obtained after a comparable single oral dose of aureomycin, in which levels of 0.3 to 2.5 microgm. per ml. of serum were obtained in adults[2] and levels of 1.08 to 2.00 microgm. per ml. of serum were noted in children receiving 22 mg. per kg.[3]

*Cultures were supplied through the kindness of Dr. J. H. Dornbush of the Lederle Laboratories.

Serum Levels of Aureomycin after Multiple Rectal Administration

Table 2 summarizes the results in those patients who received multiple doses of 20 to 80 mg. per kg. per dose. Again there was a lapse of four to six hours before significant levels were obtained. There was wide variance in the six-hour serum levels, with a range of 0.1 to 2.0 microgm. per ml. at six hours, and a mean value of 0.6 microgm. per ml. The highest sustained level on the multiple-dose regime was 1.6 microgm. per ml., which was obtained in L. A.. a boy weighing 35 kg. who received 1500 mg. of aureomycin every six hours for forty-eight hours (43 mg. per kg. per dose) and when serum was measured at eighteen, twenty-four, thirty-six and forty-eight hours after the initial dose. It will be noted that, despite the relatively high doses of aureomycin in these cases, values of 0.4 to 1.6 microgm. per ml. of serum with an average value of 0.9 microgm. per ml. were the highest obtained after eighteen to twenty-four hours of multiple-dose therapy. This again represents considerable variation and does not compare favorably with oral dosage.[2]

Comparison of serum and urine levels was made in 4 patients. This is shown in Table 3, with the total amounts of aureomycin recovered. Again a marked variation is noted in these patients, with optimal values in patient L. A., who maintained high serum levels six hours after his third, fourth,

TABLE 3 (*Concluded*).

PATIENT	24 HOURS AFTER INITIAL DOSE		36 HOURS AFTER INITIAL DOSE		48 HOURS AFTER INITIAL DOSE		54 HOURS AFTER INITIAL DOSE		TOTAL DOSE OF AUREOMYCIN	TOTAL AMOUNT OF AUREOMYCIN RECOVERED IN URINE
	URINE	BLOOD	URINE	BLOOD	URINE	BLOOD	URINE	BLOOD		
	microgm./ml.		*microgm./ml.*		*microgm./ml.*		*microgm./ml.*		*mg.*	*mg.*
J. S.	128	.4	4	—	—	.2	—	—	4,000	111
L. A.	80	1.6	160	1.6	80	1.6	16	—	12,000	938 (8¼%)
R. L.	16	.4	4	.2	—	<.2	—	—	2,000	93
P. H.	.5	.4	5	<.2	.5	—	—	—	2,000	2

sixth, seventh and eighth doses and in whom 8 per cent of the aureomycin was recovered in the urine. Minimal values were obtained in patient P. H., with the highest serum value 0.8 microgm. per ml. at six hours after his second aureomycin dose. In this patient only .001 per cent of the aureomycin was recovered in the urine.

Side-Reactions

Approximately 65 to 75 per cent of the patients complained of tenesmus, and at least 18 to 20 per cent complained of pain, eventually expelling the medication within one hour after administration. The latter group was not included in the serum- and urine-level assay tabulations. Four patients receiving multiple aureomycin dosages in suppository form were proctoscoped twenty-three hours after cessation of therapy. These 4 patients were noted to have injection of the rectal mucosa, and in 1 patient a small 0.5-by-1-cm. ulceration was noted.

Summary

Data are presented on single and multiple rectal doses of aureomycin, including serum levels and urinary excretion. Twenty to 80 mg. per kg. per dose of the drug was given to 20 children from four to twelve years of age.

Even with the large doses used, there was marked variability in the serum levels obtained; most of the patients showed inadequate serum levels of aureomycin.

Measurement of urinary excretion of aureomycin in 4 patients gave indirect evidence of poor absorption of the drug from the rectum.

Approximately three fourths of the subjects had tenesmus and pain, and almost a fourth of them expelled the aureomycin within one hour. Four who were proctoscoped showed local mucosal irritation from the drug.

It is believed, because of the poor absorption, wide variance in serum levels obtained, unpleasant and toxic side-effects and the large dosage required, that despite the occasional achievement of low therapeutic levels rectal administration of aureomycin is an unsatisfactory method of treatment.

References

1. Dornbush, A. C. Personal communication.
2. Brainerd, H. D., Bruyn, H. B., Jr., Meiklejohn, G., and Scaparone, M. Assay of aureomycin in body fluids: observations on individuals receiving aureomycin. *Proc. Soc. Exper. Biol. & Med.* **70**:318-321, 1949.
3. Whitlock, C. M., Jr., Hunt, A. D., Jr., and Tashman, S. G. Studies on administration, absorption, distribution and excretion of aureomycin in children. *Pediatrics* **6**:827-842, 1950.

THE EFFECT OF VOLATILE 1-CYCLOHEXYL-2-METHYLAMINOPROPANE ("BENZEDREX" INHALER) ON PATIENTS WITH CORONARY ARTERIOSCLEROSIS*

Joshua B. Burnett, M.D.,† and Sven M. Gundersen, M.D.‡

HANOVER, NEW HAMPSHIRE

THIS paper is a report on a controlled study of the effects of a new sympathomimetic drug on patients with coronary arteriosclerosis. The drug, 1-cyclohexyl-2-methylaminopropane, is used commercially in a volatile form in an inhaler ("Benzedrex" inhaler) for its vasoconstrictive and detumescent effect on the nasal mucous membrane. By using excessive inhalation doses we have tried to bring out any of its deleterious side-effects on the cardiovascular system of patients with arteriosclerotic heart disease in order to determine whether or not they could safely use the inhaler in the treatment of upper-respiratory infections.

In 1939 Peters and Faulkner[1] tested a series of cardiac patients and normal controls with another inhaler containing volatile amphetamine ("Benzedrine" inhaler). One patient, out of 28 with arteriosclerotic heart disease, repeatedly suffered an attack of angina pectoris every time she inhaled the drug in a little over twice the recommended therapeutic dose; its use in such patients therefore had to be restricted. The present drug differs from amphetamine in that it is a cyclohexylalkylamine rather than a phenylalkylamine. Moreover, in this substance a methyl group replaces one hydrogen atom on the amine nitrogen. Several investigators[2-5] have shown that this compound has approximately half the vasopressor potency of amphetamine and that it has decidedly less stimulating effect on the central nervous system. It has no positive inotropic activity on the isolated heart muscle of the frog. It does, however, have a vasoconstricting and detumescent effect comparable to that of amphetamine on the nasal mucosa of dogs. For these reasons a trial of the drug in patients with arteriosclerotic heart disease seemed warranted.

Method

Twenty patients with typical angina pectoris due to coronary arteriosclerosis were tested. No patient was included in whom the diagnosis was doubtful. Ten of the patients had had well documented myocardial infarctions, and in all of them an attack of angina pectoris could be brought on by moderate exertion at the time of the test. Three patients were tested a few days and 2 patients were

*From the Mary Hitchcock Memorial Hospital and the Hitchcock Clinic, Hanover.

†Instructor in medicine, Dartmouth Medical School; assistant in medicine, Hitchcock Clinic.

‡Assistant professor of medicine, Dartmouth Medical School; staff member, Hitchcock Clinic and Mary Hitchcock Memorial Hospital.

tested five weeks after the occurrence of a fresh myocardial infarction.

At the commencement of each test there was a rest period of ten to twenty minutes, while the pulse and blood pressure stabilized and a control electrocardiogram was taken. The three standard limb leads and Lead V_4 were used each time. The subject then inhaled as deeply as possible, six times in each nostril, through a control inhaler,* which contained oil of lavender 105 mg. and menthol 25 mg. This substance is the same as the "Benzedrex" inhaler but lacks the active amine. Immediately after this an electrocardiogram was taken and the patient rested again for five minutes. At this point, with the patient well trained in the procedure, he inhaled deeply at least six times through each nostril from the "Benzedrex" inhaler, which contained, in addition to the materials in the control inhaler, 300 mg. of the active amine. Again an electrocardiogram was taken immediately and also fifteen minutes after the inhalations. Pulse and blood-pressure readings were taken at approximately two-minute intervals throughout the entire test, and any ectopic beats were noted. Any complaints of the patient were also recorded. The inhalers were all uniform in appearance and were numbered for identification. Fresh inhalers were used for each patient. The patients were not specifically warned to expect an angina attack, nor were they questioned about chest pain until the test was completed. We told them that the object of the test was to observe the effect of a new medicine on the electrocardiogram, thus avoiding as much as possible any suggestion of chest pain.

It has been estimated, in an earlier study,[6] that the average inhalation volume in 108 patients was 800 cc. of air in a total of four inhalations (two in each nostril). The range of inhalation volume was 200 to 2500 cc. It has also been calculated[6, 7] that the average dose (800 cc. of air at 75°F. taken from an inhaler at the rate of 100 cc. of air per second) contains "Benzedrex" 0.5 mg., oil of lavender 0.097 mg. and menthol 0.014 mg.

In our study the patients inhaled at least three times the recommended dose calculated above; thus they received approximately 1.5 mg. of the active amine in the entire test. If for some reason the patient did not inhale deeply, he was asked to inhale further until we were convinced that he had taken an amount in excess of the recommended dose.

*The control inhalers and the "Benzedrex" inhalers were kindly supplied by the Smith, Kline and French Laboratories, Philadelphia, Pennsylvania.

Results

In none of these patients was an attack of angina pectoris precipitated, nor was there any significant change in the pulse or blood pressure (Table 1). In 2 patients a few ventricular ectopic beats were noted electrocardiographically that were not seen in the control periods. The electrocardiograms showed no other significant changes after the inhalation of the amine.

While using the inhaler containing the amine, all patients eventually complained of nasal irritation, probably because of the excessive doses employed in the tests. In some cases this caused considerable discomfort and was accompanied by coughing.

Table 1. *Changes in Pulse and Blood Pressure.**

Observed Changes in Blood Pressure	After Use of Control Inhaler			After Use of "Benzedrex" Inhaler		
	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Rate	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Rate
Average rise	6.2	2.4	1.6	7.7	3.2	2.6
Maximum rise	20	10	8	16	10	8
Minimum rise	0	0	0	0	0	0

*In only 1 patient did these changes last more than four minutes; the systolic blood pressure rose 20 mm. of mercury for six minutes after the *control* inhaler and only 8 mm. after the "Benzedrex" inhaler.

Discussion

It was predicted from the physiologic data cited above that the cyclohexylalkylamines such as the one tested here would be less likely to produce a pressor response or other stimulatory effects on the cardiovascular system than were the phenylalkylamines. In normal use a very small dose of the drug is taken; even with the excessive doses used in this series of patients, all of whom had severe arteriosclerotic heart disease, no untoward side-effects were observed.

Conclusions

Excessive doses of volatile 1-cyclohexyl-2-methylaminopropane failed to produce any undesirable side-effects such as angina attacks or vasopressor responses in 20 patients with severe angina pectoris due to coronary arteriosclerosis. No significant electrocardiographic changes were observed.

References

1. Peters, C. M., and Faulkner, J. M. Circulatory effects of volatile amphetamine (benzedrine inhaler). *Am. J. M. Sc.* **198**:104-107, 1939.
2. Lands, A. M., Nash, V. L., Granger, H. R., and Dertinger, B. L. Pharmacologic acitivity of N-methyl-β-cyclohexylisopropylamine hydrochloride. *J. Pharmacol. & Exper. Therap.* **89**:382-385, 1947.
3. Ellis, S. Action of sympathomimetic amines on isolated heart of frog. *J. Pharmacol. & Exper. Therap.* **96**:365-371, 1949.
4. Marsh, D. F., and Herring, D. A. Comparative pressor activity of optical isomers of cyclohexylisopropylamine and cyclohexylisopropylmethylamine. *J. Pharmacol. & Exper. Therap.* **97**:68-71, 1949.
5. Fellows, E. J., Macko, E., and McLean, R. A. Observations on several cyclohexyl- and phenyl-alkylamines. *J. Pharmacol. & Exper. Therap.* **100**:267-272, 1950.
6. Johnson, R. N., Baltzell, E. D., and Muller, W. P. Personal communication (from Smith, Kline & French Laboratories, Philadelphia).
7. Simpson, N. A., and Simon, E. Experimental determination of amount of "benzedrine" in therapeutic dose from "benzedrine inhaler." *Am. J. Pharmacol.* **109**:343-347, 1937.

MEDICAL PROGRESS

DISEASES OF THE THYROID GLAND (Part II)

OLIVER COPE, M.D.*

BOSTON

TUMORS

Lumps in the thyroid gland are a problem commonly plaguing the physician. It is not merely that these lumps are unsightly or press on neighboring structures; these aspects of the problem can easily be solved. They are a problem because although the majority of them are innocent involutional bodies an occasional one is a malignant tumor. They are a problem because it is not yet known, short of exposing it at operation, how to ascertain whether or not a lump harbors a malignant lesion or a lesion that may become malignant. To make decision more difficult, clinicians do not agree about the clinical significance of cancer of the thyroid. Pathologists still differ in opinion concerning the neoplastic nature of certain thyroid lumps and concerning some of the microscopical criteria of malignancy. Although an exciting beginning has been made in the experimental production of thyroid tumors, so little is understood of the etiology of the neoplastic lesions that concepts of origin differ. Unlike the control of endemic goiter with iodine, no discernible headway has been made in the prevention of true thyroid neoplasms. Finally, in the light of the present availability of radioactive iodine there is confusion about what constitutes proper therapy.

Significance of Cancer in Goiter

How often and in what kinds of thyroid lumps is cancer likely to be found? The advent of the two new nonsurgical treatments for hyperthyroidism has freshened interest in this question of the clinical significance of carcinoma in goiter. The criticism of both the radioactive-iodine and thio-compound therapies on the ground that they may be carcinogenic has made it essential that the spontaneous incidence of cancer be determined. Only through knowing how often cancer is found in the various types of goiter in patients who have received no treatment will it be possible to compute any carcinogenic effect of the therapies. It is therefore not surprising that in the past seven years this question of the clinical significance of thyroid cancer has frequently been debated at medical conferences and in a number of written reports.

Prior to 1941 it was well recognized that cancer was a lesion of the thyroid that required attention and therapy. Carcinoma was not uncommonly encountered in endemic and nodular goiter; hence it was generally considered wise to operate on the majority of patients with nodular, or, as it is often called, adenomatous goiter.[138] The greater incidence in goiters consisting of a single nodule had been recognized.[139, 140] On the other hand, the rare occurrence of cancer in the goiters of patients with hyperthyroidism seems to have been so shielded, — perhaps by the many difficulties inherent in the surgical management of the period that it had become a clinical axiom that hyperthyroidism excluded the presence of true cancer.[141]

Since 1941 much new evidence has come to light concerning the incidence of cancer in goiter. In 1944 and 1945 three papers appeared from widely separated areas of the United States calling attention to the potential hazard of overlooking a cancer in nodular goiter. Ward[142] reported from San Francisco an incidence of cancer of 4.8 per cent in nodular goiter. Cole and his co-workers,[143] from Chicago, an endemic goiter area, were encountering the much higher incidence of 17.1 per cent in nontoxic nodular goiter, with 7.2 per cent in all nodular goiter, both toxic and nontoxic. Hinton and Lord[144] recorded a 7.6 per cent incidence of cancer in apparently benign goiters encountered in New York. (The aforementioned authors are surgeons.)

With the exception of the incidence reported by Cole and others, which was higher than any previously recorded, the statistics in these reports occasioned no surprise among surgeons. To two groups of internists, on the other hand, the reported incidence of carcinoma was unbelievably high. These internists were treating patients with hyperthyroidism; they were not encountering goiters with any evidence of harboring a cancer. The disparity between the reports and their own observations warranted study. Two articles were published in the *New England Journal of Medicine* in 1947, as a result.

The first paper was by VanderLaan,[145] who reasoned that if carcinoma of the thyroid was a significant disease it should be found as a cause of death. Accordingly, he studied the incidence of carcinoma of the thyroid as a cause of death in autopsies at 3 Boston hospitals. The incidence was exceedingly low, and in an attempt to explain the disparity between the post-mortem and clinical statistics reported by the others he suggested that the microscopical criteria of cancer of the thyroid had been

*Associate professor of surgery, Harvard Medical School; visiting surgeon, Massachusetts General Hospital.

differently applied, thus leading to too common a diagnosis of carcinoma.

The second paper was by Rogers, Asper and Williams, from the Thorndike Memorial Laboratory of the Boston City Hospital.[146] Their review of the records of patients admitted for goiter at 1 Baltimore hospital and 2 Boston hospitals also disclosed an incidence of carcinoma considerably lower than that reported by the surgeons — only 2.29 per cent of all goiter cases.

Both VanderLaan and Williams and his colleagues gathered their statistics in part from the files of the Massachusetts General Hospital. Since their opinions were at variance with that of the Thyroid Clinic of this hospital, it was essential that an analysis be made of the comprehensive experience of this hospital and that their presentations be reviewed in the light of the analysis.[122] It became clear, first of all, that VanderLaan had looked in the wrong file drawer. Patients with cancer of the thyroid rarely die in the hospital; they either are relieved by operation and irradiation or choke slowly at home. That is the reason that he had found in the autopsy list so few of the cases of carcinoma of the thyroid that were treated at the Massachusetts General Hospital during the period of his survey.

Secondly, Williams had diluted the incidence of carcinoma of the thyroid encountered at the Massachusetts General Hospital by including hyperfunctioning goiters as well as the nontoxic type. As has already been intimated and as we shall see later, cancer is rarely found in patients with hyperthyroidism. Although Williams and others may not have presented their statistics in a light best demonstrating the significance of cancer in nodular goiter, they did well to question the logic of current surgical treatment of nodular goiter designed to prevent the development of cancer of the thyroid gland. This question will also be considered later.

These papers by VanderLaan and by Rogers, Asper and Williams brought forth a succession of rebuttals.[122, 147-151] The Mayo Clinic has also reviewed its more recent experience and compared it with its earlier records in search for any change in incidence.[123] It seems that cancer of the thyroid gland was firmly established as a disease to be reckoned with. These reports generally agree on the following points:

Carcinoma is encountered most frequently in a goiter consisting of a single nodule.[122, 148, 150] This should occasion no surprise, since by definition cancer is neoplasia, and neoplasia means an autonomous growth of one part without regard for the remainder of the tissue. The actual incidence of cancer reported in nodules that on physical examination appeared to be single varied from 10 to 24 per cent. These statistics do not, of course, imply that the finding of a single nodule on physical examination means cancer. The lesion in such a finding can also be a benign neoplasm, an involutional nodule, a cyst or localized thyroiditis.

Nodular goiter is the next most likely type in which carcinoma may be found. The disease process of nodular goiter affects to some extent all of the glandular apparatus and therefore was initially a hyperplasia. The malignant degeneration, however, is not diffuse but arises in one area, apparently as a complication. The incidence of cancer varies in the series reported from 4 to 17 per cent, the majority reporting approximately 8 per cent. This statistical incidence means that a patient with a nodular goiter, that is, a diffuse enlargement of the thyroid gland punctuated here and there by nodules, has an 8 per cent chance that one of his nodules is a carcinoma. Hypersecretion by the goiter with hyperthyroidism appears to diminish the likelihood of cancer.[123]

Endemic, or iodine-deficient goiter, appears to have the same incidence of cancer as nodular goiter.[123, 138, 148] Both goiters are believed to start with the same hyperplastic process; in endemic goiter the hyperplasia is known to be an effort to compensate for the lack of iodine.

In the goiters of hyperthyroidism and thyroiditis the statistical incidence of cancer is much lower. At the Mayo Clinic, cancer is encountered in the nodular goiters with hyperthyroidism in 1.2 per cent of cases.[123] In the diffuse hyperplastic goiters of Graves' disease the incidence is but 0.4 per cent. At the Massachusetts General Hospital a survey of a recent ten-year period gave an incidence of 0.8 per cent in all goiters with hyperthyroidism.[122] In the thyroid enlargements due to thyroiditis, the incidence of cancer is apparently negligible. Cancer has been found associated with thyroiditis in only a few isolated cases. It can be suspected that the two diseases were coincidental and that the thyroiditis did not play an etiologic role.

Natural History of Thyroid Cancer

Few students of cancer of the thyroid gland agree on terminology and classification. There is a variety of tumors, each with a different behavior, and not infrequently the tumors are of mixed type. Classifications based on microscopical appearance are unsatisfactory, as the behavior of the tumor often does not coincide with the microscopical findings. For example, a tumor wildly hyperplastic on microscopical section may have a sluggish growth clinically; a tumor with well differentiated follicles, even containing colloid, may be stubbornly invasive and its cells may be functionally so inactive that radioactive iodine is scarcely absorbed by them.

What really concerns us in treatment of cancer is the biologic behavior of the tumors. Much has recently been learned about the functional capacity of the cells of the various tumors through the use of radioactive iodine, total thyroidectomy, TSH and

thiouracil. This functional capacity added to the clinical behavior of the tumors gives a much wider view of their biology. It now appears advantageous to stress biologic behavior rather than microscopical appearance.

When thyroid cancer is surveyed from the point of view of biologic behavior, three distinct groups emerge. These types can, by their ways of growing and by their functional activity in producing the thyroid hormone, be distinguished from each other, from nodular goiter and from benign adenomas. The first group follows the general pattern of cancers of other organs of the body. It is a disease of middle and older age, the frequency increasing with age. In this group are the undifferentiated cancers and adenocarcinomas. The undifferentiated cancers include the small-cell and giant-cell carcinomas. They grow wildly and rapidly and spread principally by direct invasion but also through the lymphatics and the blood stream. They are sometimes confused with rapidly growing sarcoma and lymphoma. (They are also confused with thyroiditis.) They yield poorly to operative treatment and are sensitive to irradiation only on the first course of treatment; recurrence is rapid. The prognosis is bad; few patients survive as long as two years after the diagnosis has been established.[152]

The adenocarcinomas include the alveolar type and many of those called follicular carcinoma. The cells of these cancers tend to differentiate toward the characteristic acinar pattern of the thyroid. Their invasion is also predominantly local, but they too spread through the lymphatics and the blood stream. The metastasis does not always resemble the primary growth; when well differentiated it may be confused with the metastasis from a primary tumor of the third group. The rate of growth of primary tumor and metastases varies as does that of adenocarcinomas of other organs such as those of stomach and large bowel.[153] The group also includes the epithelial carcinomas. Treatment rarely succeeds in complete cure. The rapidity of recurrence varies.

These cancers have little or no functional capacity. They do not support thyroid function when the normal thyroid tissue has been removed. The undifferentiated cancers rarely have a recognizable avidity for radioactive iodine. Only those adenocarcinomas with well formed follicles are able to concentrate clinically measurable quantities; not all of these are able to do so. Their functional activity is less likely to be changed by total thyroidectomy, TSH and thiouracil than is that of those in the third group.

In the second group are the papillary adenocarcinomas. They are the commonest. They constituted 60 per cent of the recent series of the Mayo Clinic.[128]

The papillary cancers are biologically different from the others. They lack the typical age distribution of malignant disease. They are the only cancers of the thyroid that are encountered in children, yet they are no more malignant in childhood than in middle or old age. They appear to be equally distributed throughout all decades of life. This broad age incidence without variation in the nature of malignancy has no counterpart in a cancer of any other organ.

The papillary cancers are of sluggish growth. In spite of the fact that many appear microscopically to be wildly growing, they are generally slow to invade locally. They are prone, however, to metastasize early through the lymphatics to the lymph nodes, but they may be confined for months to years to the lymph nodes before they spread farther. Because of their slowness to invade locally and their habit of staying long within the lymph nodes, they have a high curability rate through surgical extirpation, and the prognosis is good when an adequate operation is undertaken.[154] They are insensitive to irradiation.

In contrast to the papillary-like hyperplasia of Graves' disease treated with thiouracil, to which they bear a superficial resemblance, the cells of the papillary cancer have a low functional activity. In a group of 16 so tested, only 2 showed a measurable uptake of radioactive iodine.[155] The functional activity of only 1 of them was increased by total thyroidectomy and thiouracil.

The third type of thyroid cancer is so peculiar and so unlike a tumor of any other organ that it still has no acceptable name. It is called by some "benign metastasizing goiter" or "metastasizing adenoma." The primary lesion in the thyroid gland is grossly so benign that distant metastases are not suspected. Microscopically, too, suspicion is often not aroused. It gives rise, however, to blood-borne metastases that avoid the lung and grow characteristically in bone, sometimes as a single metastasis but usually in multiple foci. The metastasis grows slowly and is usually encapsulated like its parent tumor. The cells also are differentiated like the primary tumor. It is found characteristically in people in the later decades of life; it therefore follows the age distribution of cancer. It is the least frequently encountered type of malignant thyroid tumor. Some of the Hürthle-cell adenomas probably belong in this group.[156]

The functional capacity of the cells of this type of cancer stand out in contrast to those of the other two types.[152, 157, 158] The cells are capable of normal or perhaps better than normal function. A metastasis of perhaps not more than 30 gm. can supply the hormone requirement of the patient. If the mass of metastatic tissue is large, the patient may suffer from hyperthyroidism even though the primary lesion and all of the undiseased thyroid gland in the neck have been resected.[158, 159] The cells of this cancer are found to have a high avidity for radio-

active iodine. The bony metastases may be disclosed by the radioactive emanations.

Cancers of mixed types are not uncommon. Cell structure may differ widely in varying areas of the same tumor, suggesting that different parts of the same tumor are growing at different rates. Most commonly a papillary tumor and an adenocarcinoma may be mixed. Occasionally an undifferentiated cancer appears to be superimposed on an adenocarcinoma. Carcinomas of the third group, in contrast, seem to live apart from the other two.

Failure to differentiate these biologically different types of cancer has led to confusion and sometimes to misunderstanding about the effectiveness of therapy. Because operation cures what appears to be a wildly growing papillary cancer does not mean that a similar operation will prove effective against an undifferentiated carcinoma. Conversely, because external irradiation is effective in melting an undifferentiated cancer, irradiation, even in huge doses, will not exterminate a papillary cancer. Nodules of papillary cancer have been found to lie dormant in lymph nodes for many years after heavy irradiation, only to break forth later and continue their spread.[65]

Failure to recognize the sluggish growth of the papillary cancer has led to the concept that the papillary cancers of hyperthyroidism are not truly malignant.[123] However, some of these papillary cancers encountered in patients who have had longstanding hyperthyroidism have been found to invade the trachea, esophagus and carotid sheath. Such invasiveness, it is true, has been found in patients in the older age group, suggesting that sometimes these cancers, although papillary in form, may be biologically more like a cancer of the first group.[65]

We have only vague notions about the etiology of thyroid cancer. The malignant lesion not infrequently appears to start *de novo* — that is, in a previously normal gland. This is true of all types. The occurrence, however, of a cancer in a goiter known to have been longstanding, as in nodular or endemic goiter, suggests that the cancer is a late phase in the disease process and that the same stimulus from which the nodular goiter arose is ultimately the cause of the cancer. Although this latter concept appears to fit the natural history, it is hard to reconcile it with what is believed about the thyrotropic stimulus in nodular goiter as opposed to hyperthyroidism. In hyperthyroidism the thyrotropic stimulus of the anterior pituitary lobe is believed to be stronger than in nodular goiter, yet the incidence of cancer is lower. Perhaps it is the chronicity of the stimulus that counts.

A commonly held concept of the origin of thyroid cancer is that it is a degeneration of a previously benign neoplasm.[150, 160] It is true that a malignant lesion is occasionally seen grafted, as it were, onto one area of an otherwise benign lesion, but it is hard to believe that all malignant neoplasms start in this way, since the primary lesion of many of the papillary cancers, for example, may be very small — not more than 2 to 4 mm. in diameter.[152] In these cases no sign of a previously existing benign adenoma is found. This concept of a preliminary benign lesion does not, of course, exclude the thyrotropic theory.

The thyrotropic theory of the etiology of thyroid cancer has recently received much support from the studies of experimental tumors.

Experimental Tumors

The possibility that both the thiouracil drugs and radioactive iodine might produce tumors of the thyroid gland has been the subject of extensive investigations in laboratory animals since 1943. Spurred on in part by interest in the phenomenon of the intense hyperplasia induced in the thyroid by the thio-compounds and in part by the criticism that the thiouracil treatment might be carcinogenic, four independent groups of investigators have studied in rats and mice the tumor-forming properties of the thiouracil compounds.[116, 161-169] Thiouracil or a related compound has been fed to the rats and mice in large doses over periods of many months. In some experiments a chemical carcinogen or partial thyroidectomy has been added to the experiment. The studies, started soon after the introduction of thiouracil in the treatment of hyperthyroidism by Astwood in 1943, are remarkable in many ways.

First, the findings and conclusions of the groups are in extraordinarily close agreement. This is doubly remarkable in that the groups and their animal stocks are unrelated. Bielschowsky started his work in London; Money and Rawson began theirs in Boston; Purves and Griesbach live in New Zealand and Morris and his co-workers in Bethesda, Maryland.

Secondly, the tumors that appear in succession in the thyroid glands of these animals as the drug is continued month after month simulate all the nodules and tumors found in hyperplastic and nodular goiters in the human being. Solid embryonal-like tumors, papillary cystadenomas, involutional colloid nodules and, finally, carcinomatous lesions have been encountered. Even the hemorrhages and the healing with fibrosis seen in human goiter are encountered in these animals.[167]

Thirdly, although the simultaneous administration of a chemical carcinogen, not capable in itself of producing thyroid lesions, may accelerate the appearance of the benign lesions, it is the thyroid-stimulating action of the anterior pituitary lobe that is essential to the production of both benign and malignant tumors.[162, 163]

Fourthly, the malignant tumors are capable of autonomous growth as transplants in other animals.[166] Such autonomy is a characteristic of the

malignant growths of the human thyroid gland.[170, 171] It may be considered biologic proof that these experimental lesions are truly carcinomatous.[172, 173]

Finally, tumors of the thyroid gland have been experimentally produced for the first time. The consistency with which they can be reproduced affords experimenters a method of studying the pathologic biology of thyroid tumors.[174]

The story of these experimental tumors does thus far lend support to the concept that an excess of the thyroid-stimulating hormone of the anterior pituitary lobe is a cause of thyroid cancer. How far experiments in rats and mice may be translated to the human being is problematic. Tumor susceptibility may well differ between rodents and the human being, and it would be unwise to give up using the thiouracil drugs in the human being on the assumption that they will ultimately produce malignant tumors. Present clinical evidence is against this assumption. Perhaps, as has already been said in the discussion of the therapy of hyperthyroidism, it will be wiser to limit the use of these drugs to the minimum effective dose for the shortest effective time.

Experiments have recently been carried out concerning the carcinogenic activity of radioactive iodine. Benign and malignant tumors have been induced in rats but not with the same consistency as those induced by the thiouracil drugs.[175-177] Doniach planned his experiments to combine the radioactive iodine with thiouracil feeding. Many benign but no malignant tumors were encountered. A benign tumor was occasionally induced when the radioactive iodine was given alone. The radioactive iodine seemed merely to enhance the benign-tumor production of the thiouracil — an action similar to that of the chemical carcinogen. Doniach therefore concluded that the beta rays of the iodine have a carcinogenic action. He realized, however, that the radioactive iodine might also have indirectly induced tumor formation by increasing the thyrotropic stimulus. The radiation presumably reduces the number of secreting thyroid cells; the remaining cells are then exposed to a greater thyrotropic stimulus.

Goldberg and Chaikoff have also investigated the carcinogenic action of radioactive iodine on the thyroid gland of rats.[176] Twenty-five rats were given a large, presumably necrosing, dose of the iodine. One and one-half to two years later, malignant tumors were found in 7. In microscopical appearance and manner of metastatic spread the tumors resembled the adenocarcinomas and undifferentiated and papillary carcinomas encountered in the human being. They invaded lymph nodes, lungs, bones, the adrenal gland and subcutaneous tissue. Benign adenomas were also found in 5 of the rats. These authors believe they excluded the thyrotropic stimulus as the indirect source of carcinogenic action by feeding control rats propylthiouracil during the same experimental period. In these control animals they found only benign adenomas and the intense thyroid hyperplasia that results from this drug.

Maloof, Dobyns and Vickery[177] have also sought to induce tumors in the thyroids of rats with radioactive iodine, but they have been unsuccessful. By calculation their maximum dose was three quarters of that used by Goldberg and Chaikoff, yet it completely destroyed the thyroid gland and all the rats died in myxedema within the first year. Thirty animals receiving one third of the maximum dose were sacrificed eighteen months after the irradiation; no tumors were found. This dose had been large enough to impair but not destroy the functional activity of the gland.

The experiments with radioactive iodine, particularly those of Goldberg and Chaikoff, occasion more concern than any of those made with the thiouracil compounds. The discrepancies between the findings of Goldberg and Chaikoff and those of Maloof and his co-workers are as yet unexplained. If Maloof and his co-workers had chosen a dose intermediate between their maximum and next lower dose and had studied their animals longer, they might perhaps have encountered tumors comparable to those found by Goldberg and Chaikoff. Certainly these experiments need further confirmation; in any case the same hesitation must be used in translating such findings to the problem of radioactive-iodine carcinogenesis in the human being. Another fact causing more worry about radioactive iodine than about thiouracil is that once the dose of irradiation is given there is no turning back. With the thiouracil compounds, the dose can always be reduced and administration of the drug terminated. The experiments with thiouracil indicate that time offers a wide margin of safety. Barring the presence of a chemical carcinogen, it takes several months to produce tumors, and the appearance of the tumors follows an orderly reproducible sequence. The benign tumors come first and the carcinomas at long last.

Treatment of Cancer

The treatment of cancer is carried out by surgery, high-voltage x-rays or radioactive iodine — or by a combination of these. Hormonal therapy through variation of the thyrotropic stimulus has only begun.

Surgery is the oldest treatment; it is still preeminent. It is the only therapy effective against the papillary cancers, the commonest of the malignant tumors. Success is also best achieved with the other cancers by excising them — but only in their early phase, before spread has taken place.

High-voltage external irradiation continues to offer palliative therapy in the undifferentiated cancers. Radioactive iodine has, on the whole, been disappointing. It has been a boon to therapy in treating the metastases of but two types of cancer —

the most differentiated of the adenocarcinomas and the uncommon well differentiated benign-appearing metastasizing adenomas. In these cancers radioactive iodine has been palliative. Real cures are still uncertain.[83, 84, 155, 157, 158, 178-180]

The aim of surgical therapy is to excise the entire malignant area. It should avoid mutilation through unnecessarily wide excision. A primary purpose of operation, therefore, is to establish the type of disease and its extent.[151] The various procedures of excision are described in a number of texts.

Surgery is also a useful adjunct to the radioactive-iodine therapy of thyroid metastases.[152, 181-184] Through resection of all the undiseased thyroid tissue as well as the primary lesion in the neck, the metastases are relieved of the strong competition by the undiseased thyroid cells for both TSH and the radioactive iodine. The greater concentration of TSH that results from this total thyroidectomy stimulates the metastases to further functional differentiation and increases their avidity for the iodine.

It is again the already well differentiated cells of the metastasizing adenomas that are most capable of being stimulated by TSH and thiouracil to further function.[179] Unfortunately, the functional capacity of the cells of the undifferentiated cancers, the more undifferentiated adenocarcinomas and the papillary cancers is seldom significantly altered. Total thyroidectomy and the administration of TSH and thiouracil thus have little practical use in the treatment of the metastases of these cancers.

Radioactive iodine can be used, instead of surgical total thyroidectomy, to destroy the competing undiseased thyroid tissue.[184] Radiation therapy takes several weeks to obliterate the resistant normal thyroid tissue, and during this time the thyrotropic stimulus is gaining in intensity. It is probable that the increased thyrotropic stimulus hastens the growth of the metastases; thiouracil certainly does so.[152, 180] Because it shortens the time of increased TSH action and because it removes the primary tumor at the same operation, surgical total thyroidectomy is to be preferred to the radiologic technic.

Treatment of Nodular Goiter

Since thyroid surgery was first used, nodular goiter has been treated by surgical excision. In order to preserve the parathyroids and recurrent nerves the surgeon has used only subtotal resection. This policy of subtotal removal, particularly when it is acted on with the idea of preventing future malignant degeneration, has been challenged by Williams and his colleagues, and it must be admitted that it seems illogical to leave behind some of the same diseased tissue to be exposed to an even greater concentration of TSH.[146] Logically, a total thyroidectomy should be performed, with the patient being maintained on thyroid medication after the operation.

Total thyroidectomy, however, is not as easy a technical procedure in nodular goiter as subtotal thyroidectomy. The presence of the goiter makes it more difficult to isolate and spare the parathyroids and nerves. Operative accidents are more frequent.[185]

Rienhoff has suggested treating nodular goiter with desiccated thyroid.[186] This therapy seems to have received inadequate attention. Incapable of dissolving adenomas and often ineffective in resolving the larger involutional nodules, thyroid medication does dissipate small involutional goiters in the early phase of their development and the hyperplastic regrowth of remnants that follows subtotal thyroidectomy.[65, 122]

The available evidence suggests that thyroid therapy is most effective when the patient is hypothyroid. The thyroid medication presumably achieves its result by depressing the anterior pituitary lobe. In view of the clinical concept concerning TSH and tumor formation and the supporting experimental evidence, this therapy of nodular goiter is logical. If the goiter and its nodules do not melt away, surgical therapy is indicated. If operation is undertaken with the idea of preventing later malignant degeneration, then logically the operation should be a total thyroidectomy. It should be recalled, however, that this operation must be painstakingly carried out if damage to the parathyroids and nerves is to be avoided.[154, 185]

Thyroiditis

No consideration of tumors of the thyroid is complete without mention of acute and chronic thyroiditis. Occasionally an acute infectious process, its etiology remains undetermined in the majority of cases.[187-190] Despite the claims for thiouracil or thyroid medication, a satisfactory medical treatment has not been evolved.[191, 192] Radioactive iodine offers no help; it would primarily affect the thyroid cells rather than the stroma and only increase the hypothyroidism. Although external irradiation is held by some to be sound treatment,[193] it should not be used until the diagnosis has been established by the passage of time or an adequate biopsy. Unless care is taken, a rapidly growing undifferentiated carcinoma can be mistaken for thyroiditis. Surgery alone assures a correct diagnosis; operative resection is therefore the best resort if the tumor mass grows too large for comfort.[194]

References

138. Pemberton, J. deJ. Malignant lesions of thyroid gland: review of 774 cases. *Surg., Gynec. & Obst.* 69:417-430, 1939.
139. Lerman, J. In Means.[141] Pp. 466 and 467.
140. Lahey, F. H. Carcinoma of thyroid. *Am. J. Roentgenol.* 46:469-475, 1941.
141. Means, J. H. *The Thyroid and Its Diseases.* First edition. 602 pp. Philadelphia: J. B. Lippincott Company, 1937. P. 482.
142. Ward, R. Symposium on surgical lesions of thyroid; malignant goiter. *Surgery* 16:783-803, 1944.

143. Cole, W. H., Slaughter, D. P., and Rossiter, L. J. Potential dangers of nontoxic nodular goiter. *J. A. M. A.* **127**:883-888, 1945.

144. Hinton, J. W., and Lord, J. W., Jr. Is surgery indicated in all cases of nodular goiter, toxic and nontoxic? *J. A. M. A.* **129**:605, 1945.

145. VanderLaan, W. P. Occurrence of carcinoma of thyroid gland in autopsy material. *New Eng. J. Med.* **237**:221, 1947.

146. Rogers, W. F., Jr., Asper, S. P., Jr., and Williams, R. H. Clinical significance of malignant neoplasms of thyroid gland. *New Eng. J. Med.* **237**:571-576, 1947.

147. Anglem, T. J., and Bradford, M. L. Nodular goiter and thyroid cancer. *New Eng. J. Med.* **239**:217-220, 1948.

148. Cole, W. H., Majarakis, J. D., and Slaughter, D. P. Incidence of carcinoma of thyroid in nodular goiter. *J. Clin. Endocrinol.* **9**: 1007-1011, 1949.

149. Ward, R. When is malignant goiter malignant? *J. Clin. Endocrinol.* **9**:1031-1042, 1949.

150. Lahey, F. H., and Hare, H. F. Malignancy in adenomas of thyroid. *J. A. M. A.* **145**:689-695, 1951.

151. Berlin, D. D., and Gargill, S. L. Coexistence of diffuse toxic goiter (Graves' disease) and malignancy of thyroid. *Tr. Am. A. Study of Goiter*, 1947. Pp. 51-62.

152. Rawson, R. W. Tumors of thyroid. In Means, J. H. *Thyroid and Its Diseases*. Second edition. 571 pp. Philadelphia: J. B. Lippincott Company, 1948.

153. Frazell, E. L., and Foote, F. W., Jr. Natural history of thyroid cancer: review of 301 cases. *J. Clin. Endocrinol.* **9**:1023-1030, 1949.

154. Cope, O. Surgery of thyroid. In Means, J. H. *The Thyroid and Its Diseases*. Second edition. 571 pp. Philadelphia: J. B. Lippincott Company, 1948.

155. Dobyns, B. M., and Maloof, F. Study and treatment of 119 cases of carcinoma of thyroid with radioactive iodine. *J. Clin. Endocrinol.* **11**:1323-1360, 1951.

156. Chesky, V. E., Dreese, W. C., and Hellwig, C. A. Hürthle cell tumors of thyroid gland: report on 25 cases. *J. Clin. Endocrinol.* **11**:1535-1548, 1951.

157. Frantz, V. K., Ball, R. P., Keston, A. S., and Palmer, W. W. Thyroid carcinoma with metastases, studied with radioactive iodine. *Ann. Surg.* **119**:668-689, 1944.

158. Seidlin, S. M., Marinelli, L. D., and Oshry, E. Radioactive iodine therapy: effect on functioning metastases of adenocarcinoma of thyroid. *J. A. M. A.* **132**:838-847, 1946.

159. Leiter, L., Seidlin, S. M., Marinelli, L. D., and Baumann, E. J. Adenocarcinoma of thyroid with hyperthyroidism and functional metastases: studies with thiouracil and radio-iodine. *J. Clin. Endocrinol.* **6**:247-261, 1946.

160. Graham, A. Malignant epithelial tumors of thyroid. *Surg., Gynec. & Obst.* **39**:781-790, 1924.

161. Bielschowsky, F. Experimental nodular goitre. *Brit. J. Exper. Path.* **26**:270-275, 1945.

162. Hall, W. H., and Bielschowsky, F. Development of malignancy in experimentally-induced adenomata of thyroid. *Brit. J. Cancer* **3**: 534-541, 1949.

163. Bielschowsky, F. Role of thyroxine deficiency in formation of experimental tumours of thyroid. *Brit. J. Cancer* **3**:547-549, 1949.

164. Griesbach, W. E., Kennedy, T. H., and Purves, H. D. Studies on experimental goitre: thyroid adenomata in rats on Brassica seed diet. *Brit. J. Exper. Path.* **26**:18-24, 1945.

165. Purves, H. D., and Griesbach, W. E. Studies on experimental goitre: thyroid carcinomata in rats treated with thiourea. *Brit. J. Exper. Path.* **27**:294-297, 1946.

166. Bielschowsky, F., Griesbach, W. E., Hall, W. H., Kennedy, T. H., and Purves, H. D. Studies on experimental goitre: transplantability of experimental thyroid tumours of rat. *Brit. J. Cancer* **3**: 541-546, 1949.

167. Money, W. L., and Rawson, R. W. Experimental production of thyroid tumors in male rat. *Tr. Am. A. Study Goiter* 1947. Pp. 171-178.

168. Money, W. L., and Rawson, R. W. Experimental production of thyroid tumors in rat exposed to prolonged treatment with thiouracil. *Cancer* **3**: 321-335, 1950.

169. Morris, H. P., Dalton, A. J., and Green, C. D. Malignant thyroid tumors occurring in mouse after prolonged hormonal imbalance during ingestion of thiouracil. *J. Clin. Endocrinol.* **11**:1281-1295, 1951.

170. Dobyns, B. M., and Lennon, B. Growth and histologic changes of human thyroidal tumors transplanted into anterior chamber of eyes of guinea pigs. *J. Clin. Endocrinol.* **11**:1481-1494, 1951.

171. Dobyns, B. M., and Lennon, B. Study of behavior of human thyroidal tumors transplanted into anterior chamber of guinea pig's eye. *Ann. Surg.* **134**:984-998, 1951.

172. Greene, H. S. N., and Lund, P. K. Heterologous transplantation of human cancers. *Cancer Research* **4**:352-363, 1944.

173. Greene, H. S. N. Identification of malignant tissues. *J. A. M. A.* **137**:1364-1366, 1948.

174. Paschkis, K. E., Cantarow, A., and Stasney, J. Influence of thiouracil on carcinoma induced by 2-acetaminofluorene. *Cancer Research* **8**:257-263, 1948.

175. Doniach, I. Effect of radioactive iodine alone and in combination with methylthiouracil and acetylaminofluorene upon tumour production in rat's thyroid gland. *Brit. J. Cancer* **4**:223-234, 1950.

176. Goldberg, R. C., and Chaikoff, I. L. Induction of thyroid cancer in rat by radioactive iodine. *Arch. Path.* **53**:22-28, 1952.

177. Maloof, F., Dobyns, B. M., and Vickery, A. Effects of various doses of RaI on function and structure of thyroid of rat. *Endocrinol.* (in press).

178. Hamilton, J. G., Soley, M. H., and Eichorn, K. B. Deposition of radioactive iodine in human thyroid tissue. *Univ. California Publ. Pharmacol.* (No. 28) **1**:339-367, 1940.

179. Frantz, V. K., Larsen, W. G., and Jaretzki, A. Evaluation of radioactive iodine therapy in metastatic thyroid cancer. *J. Clin. Endocrinol.* **10**:1084-1091, 1950.

180. Rall, J. E., Miller, W. N., Foster, C. G., Peacock, W. C., and Rawson, R. W. Use of thiouracil in treatment of metastatic carcinoma of thyroid with radioiodine. *J. Clin. Endocrinol.* **11**:1273-1280, 1951.

181. Seidlin, S. M., Oshry, E., and Yalow, A. A. Spontaneous and experimentally induced uptake of radioactive iodine in metastases from thyroid carcinoma: preliminary report. *J. Clin. Endocrinol.* **8**:423-432, 1948.

182. Rawson, R. W., Marinelli, L. D., Skanse, B. N., Trunnell, J., and Fluharty, R. G. Effect of total thyroidectomy on function of metastatic thyroid cancer. *J. Clin. Endocrinol.* **8**:826-841, 1948.

183. Frantz, V. K., Quimby, E. H., and Evans, T. C. Radioactive iodine studies of functional thyroid carcinoma. *Radiology* **51**:532-551, 1948.

184. Seidlin, S. M., Rossman, I., Oshry, E., and Siegel, E. Radioiodine therapy of metastases from carcinoma of thyroid: 6-year progress report. *J. Clin. Endocrinol.* **9**:1122-1137, 1949.

185. Hermanson, L., Gargill, S. L., and Lesses, M. F. Treatment of nodular goiter. *J. Clin. Endocrinol. & Metab.* **12**:112-129, 1952.

186. Rienhoff, W. F., Jr. Microscopic changes induced in thyroid gland by oral administration of desiccated thyroid: use of substance in treatment of congenital and simple colloid goiter. *Arch. Surg.* **41**: 487-507, 1940.

187. Brenizer, A. G., Jr. Suppurative strumitis caused by *Salmonella typhosa*: report of case cured by surgery 24 years after acute enteric fever. *Ann. Surg.* **133**:247-252, 1951.

188. Statland, H., Wasserman, M. M., and Vickery, A. L. Struma lymphomatosa (Hashimoto's struma). Review of fifty-one cases with discussion of endocrinologic aspects. *Arch. Int. Med.* **88**:659-678, 1951.

189. Chesky, V. E., Dreese, W. C., and Hellwig, C. A. Chronic thyroiditis: supravital studies of surgical goiter specimens. *Surg., Gynec. & Obst.* **93**:575-580, 1951.

190. Merrington, W. R. Chronic thyroiditis: case showing features of both Riedel's and Hashimoto's thyroiditis. *Brit. J. Surg.* **35**: 423-426, 1948.

191. Crile, G., Jr. Thyroiditis. *Ann. Surg.* **127**:640-654, 1948.

192. Cantwell, R. C. Thiouracil in acute thyroiditis. *Ann. Int. Med.* **29**:730-732, 1948.

193. Schilling, J. A. Struma lymphomatosa, struma fibrosa and thyroiditis. *Surg., Gynec. & Obst.* **81**:533-550, 1945.

194. Marshall, S. F., Meissner, W. A., and Smith, D. C. Chronic thyroiditis. *New Eng. J. Med.* **238**:758-766, 1948.

Correction. In Part I of the Medical Progress Report on "ACTH and Cortisone in Dermatology" by Dr. John G. Downing, which appeared in the January 10 issue of the *Journal*, the fourth line in the last paragraph on Page 59 should read: ". . .with Cortisone the dosage was gradually decreased. . . ."

MEDICAL INTELLIGENCE

LIVING WITHOUT A BALANCING MECHANISM*

J. C.

BOSTON

ONE morning, now about four years ago, I arranged in my pajama pocket toothpaste, toothbrush, razor and shaving soap, mounted my crutches and, with towel and facecloth hung over my shoulder, made my way across the hospital ward to the lavatory. In preparation for shaving, I wrung out the facecloth in steaming hot water, spread it over my hands and then held it to my face. Thus blindfolded, I suddenly lost my balance and fell sprawling on the floor. Unhurt but surprised, I picked myself up and looked around to see if someone had jostled me. There was no one in the room. In an effort to recreate this unexpected accident, I braced myself with both hands on the edge of the sink and tried closing my eyes. Instantly I had a feeling of dizziness and nausea. After that there was no further question in my mind about the diagnosis.

Streptomycin treatment had been started nearly two and a half months earlier because it was thought that the acute arthritis in my right knee might be tuberculous. At that time relatively little information about the indications for, dosage and toxicity of this new drug had reached the medical officers in the European army of occupation. Few of us had had any opportunity to use it. The reports we were receiving, however, suggested that streptomycin was as dramatically effective in tuberculosis as penicillin in pneumococcal pneumonia.

Penicillin having proved ineffective in my case, it was decided to use streptomycin. The initial dose prescribed was 6 gm. daily, intramuscularly, with 250 mg. injected locally into the knee joint. Improvement seemed to follow, and in a week or two the dose was reduced to 4 gm. daily and the painful instillations into the joint were discontinued. Immediately prior to my return to the United States, six weeks after I became ill, the dose was reduced to 3 gm. daily. It was on the seventy-sixth day of continuous streptomycin treatment that the first symptoms of eighth-nerve involvement became evident.

I returned to my bed discouraged and frightened. At ward rounds I reported the episode in the lavatory to the medical officer in charge. His response was noncommittal, as always.

During that first day symptoms increased rapidly. Every movement in bed now caused vertigo and nausea, even when I kept my eyes open. If I shut my eyes the symptoms were intensified. At first, I found that by lying on my back and steadying myself by gripping the bars at the head of the bed I could be reasonably comfortable. Later, even in this position the pulse beat in my head became a perceptible motion, disturbing my equilibrium.

Most of us have experimented with motion pictures at home. This experience can be used to illustrate the sensations of the patient with damage to the vestibular apparatus. Imagine the results of a sequence taken by pointing the camera straight ahead, holding it against the chest and walking at a normal pace down a city street. In a sequence thus taken and viewed on the screen, the street seems to careen crazily in all directions, faces of approaching persons become blurred and unrecognizable and the viewer may even experience a feeling of dizziness or nausea. Our vestibular apparatus normally acts like the tripod and the smoothly moving carriage on which the professional's motion-picture camera is mounted. Without these steadying influences, the moving picture is joggled and blurred. Similarly, when the vestibular influence is removed from the biologic cinema system, the projection on the visual cortex becomes unsteady.

From the beginning of my illness I had resolved to try to be a patient and not the combination doctor-and-patient hybrid who often makes the care of one physician by another so difficult. Hence, at rounds that morning I had reported only my symptoms to the ward medical officer and had restrained myself from asking him to discontinue streptomycin. As I lay in bed during the rest of that day I tried to rationalize the continuing, regular visits by the nurse, who was armed with syringe and needle. Perhaps by now cultures of the joint fluid *had* grown tubercle bacilli. Perhaps loss of vestibular function *was* to be preferred to the consequences of tuberculous arthritis. From time to time I put my wristwatch to my ear to see if I could still hear its ticking and assure myself that cochlear function remained intact.

Streptomycin injections were finally discontinued two long days later. At that point my courage began to return, and there began the slow process of learning to live with a handicap. The subsequent period was one of consuming interest to me. In it I saw demonstrated how effectively the loss of one of the sensory systems of the body can be com-

*This essay, by a physician, recounting his own experiences, will appear in the forthcoming book *When Doctors Are Patients*, edited by Max Pinner, M.D., and Benjamin F. Miller, M.D., to be published in 1952 by W. W. Norton and Company.

pensated for by the other systems. My first efforts were devoted to overcoming my difficulty in reading. I found that by bracing my head between two metal bars at the head of the bed I could minimize the effect of the pulse beat, which made the letters on the page jump and blur. I gradually learned to keep my place by using a finger or pencil on the page.

Once I was again able to read, time began to pass more and more quickly. I soon persuaded myself, nevertheless, that I must try to walk. Already I had discovered, as I lay in bed, that if I turned my head from side to side while looking forward I had the sensation that the room turned around me, rather than that I was turning around in the room. This was less disturbing, however, if I focused on a distant object rather than on one but a few feet from my eyes. I had also learned that less vertigo was associated with moving about or turning over in bed if I kept my eyes closed. This maneuver had its drawback, however, in that with my eyes closed I had the giddy feeling that the bed was no longer horizontal but had been tipped up on end or on its side. On my first attempt at walking, I found that it helped to close my eyes and steady myself with both hands on the bed. Thus oriented by tactile sense, I groped my way around the bed, telling myself, despite sensations indicating the contrary, that both the floor and the surface of the bed were stationary and in a horizontal plane. Later, I learned to open my eyes, fix on a distant object to add visual to tactile orientation and move around the bed.

Progress was greatly accelerated when, at last, I was permitted to dispense with the cumbersome plaster shell that had immobilized my right leg from sole to hip. Ten days of physiotherapy restored the strength in the limb so that it no longer collapsed under me when weight was put on it. I began to take excursions around the ward, and later along the endless corridors of the hospital. In these corridors I had the peculiar sensation of being inside a flexible tube, fixed at the end nearest me but swaying free at the far end. In various places the corridors led up or down gentle inclines. On these ramps I had to learn to appreciate that I was going downhill through the sensation of strain on the extensors of my legs or that I was climbing a grade through the strain on the flexor muscles. Of course, if there was a window nearby I could corroborate the proprioceptor signals by comparing the plane of the floor with that of the horizon outside.

I learned not to do certain things. One of these was not to look at a newspaper or letter in my hand while walking. In those early days proprioceptive orientation was insufficiently developed to permit even momentary withdrawal of visual orientation. When I was allowed to go outside, I quickly found that it was imperative to restrain the impulse to look up when an airplane passed overhead until I could brace myself against a railing or tree. I discovered, when beginning to walk in open places without a nearby wall available for hasty support, that it was a mistake to slow down or stop. It was as if I were riding a bicycle; the faster I walked, the more easily could I keep a stable upright position. Indeed, I soon noticed that unconsciously I had begun to walk the same type of course that is steered by a ship's gyroscopic compass, veering first slightly to the left and then overcompensating and veering equally to the right.

During a walk I found too much motion in my visual picture of the surroundings to permit recognition of fine detail. I learned that I must stand still in order to read the lettering on a sign. These early excursions taught me a habit foreign to one of my New England background — that of greeting anyone who happened to pass in the opposite direction. Since I was unable to distinguish the familiar from the unfamiliar faces when walking, the obvious solution was to pretend to recognize everyone.

Learning to get about at night or in the darkness has been the most difficult part of convalescence. Even after considerable practice in daytime walking, I still find myself almost helpless in the dark — so helpless, in fact, that at night I have sometimes had to resort to achieving my destination on hands and knees. We rarely find ourselves totally without light, however. Thus, for example, in leaving a friend's house in the evening, a short pause outside the door usually permits accommodation so that one can see sufficiently well to maintain orientation from doorstep to automobile. My difficulties in navigation under such circumstances are still noticeable, but they can usually be passed off as due to the final highball of a convivial evening!

My life at present is little if at all affected by my disability. Since I am almost wholly engaged in research medicine and teaching, if my gait is wobbly in the evening I am not criticized as I might be if I were a practitioner making house calls. With a little extra caution I can successfully transfer a tray of glassware from one bench to another in the laboratory. I was once told that I'd have to forget some of my weekend and vacation activities. Nevertheless, I now enjoy tennis doubles as much as I once enjoyed a fast-running game of singles. On the water I am spared the sensation of seasickness and hence am a useful hand in the hot galley when the seas are choppy. For a time I was hesitant about swimming, as a well known neurologist had told me that many patients with central-nervous-system syphilis and vestibular dysfunction had drowned because they lost their orientation in the water and swam down when they thought they were coming up for air. Temptation has been too great, however. Some cautious experiments have re-

assured me that I can find the surface if I keep my head. To date I haven't been foolish enough to try swimming at night.

When I recall how completely disabled I was by the initial impact of loss of vestibular function, I am amazed that I am so little troubled at present, even though tests show no sign of recovery of that particular sensory system. Is there any man-made machine designed like the human apparatus — with so many alternate systems to accomplish its end?

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38121

PRESENTATION OF CASE

A fifty-five-year-old man was admitted to the hospital because of generalized weakness.

Five years before admission the patient first noted nocturia (1 to 2 times) and swelling of the ankles and feet that came on during the day and subsided with bed rest. These symptoms persisted. Three years prior to entry after a cold he developed painful swelling of the knees, elbows and distal interphalangeal joints of the hands, pain in the hips and a nodule over the left olecranon. The joint symptoms lasted five months, during which time he was obliged to remain in bed; following this some residual swelling of the distal phalanges and some limitation of motion of the knees remained. During this illness examination revealed a trace of albumin in the urine; elevated nonprotein nitrogen, serum phosphorus and uric acid; moderate normochromic anemia; and x-ray changes of the skull interpreted as characteristic of Paget's disease. Prior to this attack of "arthritis" there had been no weight loss, weakness or dyspnea, but during the subsequent three years he lost fifteen to twenty pounds in weight and developed slight dyspnea on exertion and progressive weakness and fatigability. The ankle edema became persistent and progressively more severe, with pitting nearly to the knees, and the nocturia increased to five to six times with accompanying polyuria. During the three years prior to entry he had several attacks of "sciatica." Tingling of the fingertips, which was first noted during the attack of "arthritis" five years prior to entry, persisted as an annoying symptom until admission. For the year prior to admission he had some difficulty in starting the urinary stream and slight burning on micturition. Three weeks before admission treatment with digitalis, low-salt diet and vitamin B_{12} injections was begun; the edema disappeared and he felt much improved. Two days prior to entry he stopped the medication because of abdominal cramps and diarrhea of two days' duration. Following this he became progressively weaker.

He had had an appendectomy at the age of twenty-two and a herniorrhaphy at the age of fifty. At the age of thirty-six he was operated on for a ruptured gastric ulcer; he had had epigastric symptoms for one and a half years prior to this operation and had been treated with calcium and bismuth powders, but since the operation he had not had any gastrointestinal symptoms or taken any medication. At the age of forty-two he had an attack of "arthritis," with redness, swelling, tenderness and limitation of motion of the left wrist and shoulders and pain in the lower back and thighs. He was treated by dental extraction, heat lamps, pills and bed rest; at the end of three months he was symptom free and had no residual deformity or limitation of motion.

Physical examination revealed a thin man in no distress. The eyes showed unusually marked limbal and subconjunctival calcification of a limbal-girdle type. The thyroid was not palpable. He was edentulous. The chest was kyphotic and there was an increase in the anteroposterior diameter. The left border of the heart was at the anterior axillary line in the fifth intercostal space. A Grade III harsh apical systolic and a Grade II basal systolic murmur, with transmission up into the neck, were present. There was thickening of the terminal phalanges of the first three fingers of both hands. There was very slight edema of the ankles and pretibial areas. The peripheral pulses were present. The prostate was three times normal size, non-nodular and non-tender.

The temperature was 98.6°F., the pulse 120 and the respirations 20. The blood pressure was 98 systolic, 40 diastolic.

A urine of specific gravity 1.009 gave a ++ reaction for albumin; the sediment contained frequent white cells and an occasional red cell and epithelial cell. A urinary Sulkowitch test was negative. Examination of the blood revealed a hemoglobin of 12 gm., a white-cell count of 12,500, with 76 per cent neutrophils, and a hematocrit of 36. The sedimentation rate was 1.1 mm. per minute (corrected). The serum sodium was 124.5 milliequiv., the chloride 91 milliequiv., the potassium 7.2

milliequiv. and the carbon dioxide 12.2 milliequiv. per liter. The blood pH was 7.33. The nonprotein nitrogen was 145 mg., the total protein 6.47 gm., with an albumin-globulin ratio of 2.1, the serum cholesterol 220 mg., the calcium 7.8 mg., the phosphorus 9.6 mg. and the alkaline phosphatase 15.4 units per 100 cc. One twenty-four-hour urine specimen with a volume of 1170 cc. contained 20 mg. per 100 cc. of calcium; another with a volume of 1240 cc. contained 73 milliequiv. of sodium, 64 milliequiv. of potassium and 18 milliequiv. per liter of chloride. A Congo red test showed 40 per cent retention in the serum. A urea clearance test was 4 per cent of normal and a phenolsulfonphthalein excretion was 5 per cent in 30 minutes and 17.5 per cent in 2 hours. A basal metabolic rate was +16 and a protein-bound-iodine determination 3.4 gamma per cent. Roentgenograms of the chest revealed normal lung fields, a normal-sized heart and calcification of the aorta and bronchial tree; the borders of the upper mediastinum were poorly defined. A barium-swallow examination showed slight displacement of the esophagus to the right. Roentgenograms of the abdomen showed scattered areas of calcification, some of which were in the region of the kidneys. The bones appeared grossly trabeculated and demineralized; the upper lumbar vertebras were osteoporotic, with increased density of adjacent surfaces. A bone survey showed widening of the shafts of the femurs, thickening of the cortical bone in the femurs and humeri, subperiosteal resorption in the humeri and punctate islands of increased density in the pubic bones. The vault of the skull and the anterior two thirds of the base of the skull showed considerable thickening, with coarse trabeculae and small islands of increased density. X-ray films of the hand showed bone destruction in the midshaft of the terminal phalanges of the first three fingers; these also appeared to be clubbed. There were destruction of the lateral portions of a number of the interphalangeal joints and subperiosteal resolution along the shafts of a number of phalanges. There was destruction of the base of the ulnar styloid process and amorphous calcification adjacent to this. An electrocardiogram revealed a tachycardia of 130, with an abnormal record due to incomplete right-bundle-branch block.

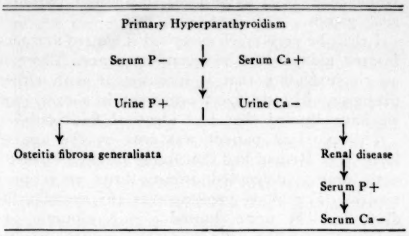
After admission there was little change in his condition. The serum sodium remained persistently low, falling to 114 milliequiv. per liter. Oral sodium-citrate therapy and a free salt intake resulted in some improvement in the acidosis, a rise in the serum sodium to 128.4 milliequiv. per liter, a lowering of the nonprotein nitrogen to 102 mg. per 100 cc. and a slight increase in ankle edema. After six days of treatment with aluminum hydroxide, 200 to 300 cc. per day, the serum calcium was 8.2 mg. and the phosphorus 6.8 mg. per 100 cc. The patient was digitalized and received a number of blood transfusions. An operation was performed on the twenty-first day.

Differential Diagnosis

Dr. Fuller Albright*: Unless I am all wrong, this case presents no diagnostic difficulties. In the first place there is no question that he has osteitis fibrosa generalisata. The question is: Which of two sequences of events led to the osteitis fibrosa generalisata? (See Tables 1 and 2.)

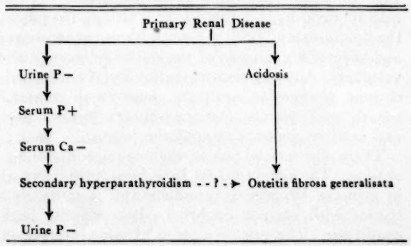
In Table 1 you will note that the first step is a primary hyperparathyroidism. This leads to a

Table 1.



characteristic disorder of the calcium and phosphorus metabolism; this in turn leads to the osteitis fibrosa generalisata. It will be further noted that the disturbance in the calcium and phosphorus metabolism may lead to renal disease and this in turn may lead to an alteration of the electrolyte pattern,

Table 2.



which one usually associates with hyperparathyroidism.

In Table 2 you will note that the initial step is primary renal disease. This leads to a decreased urinary phosphorus excretion, which in turn leads to an increase in serum phosphorus level and hence to a decrease in serum-calcium level. Since the stimulus to parathyroid function is probably a low serum-calcium level, there ensues a compensatory hyperparathyroidism, with enlargement of all four

*Physician, Massachusetts General Hospital.

parathyroid glands. This secondary hyperparathyroidism has little or no effect, since the first step in parathyroid-hormone function is an increase in urinary phosphorus excretion and since this is already limited by the renal insufficiency. To be sure, those who believe that the primary effect of parathyroid hormone is on bone tissue would have a different interpretation. (See broken arrow.)

You will note that both these sequences end with very much the same picture — osteitis fibrosa generalisata, a high serum-phosphorus level, a normal to low serum-calcium level and renal insufficiency. In the first sequence there is usually an adenoma in one parathyroid gland; in the second sequence there is hyperplasia in all four parathyroid glands.

I shall be very much surprised if we are not confronted today with the second sequence. There is no single finding that is inconsistent with either diagnosis. My strongest argument is a case that we have studied that had identical findings.[1,2]

This previous patient was seen at the age of forty-five. He had had "incurable Bright's disease" with dropsy diagnosed twenty-three years previously. The blood pressure was 165 systolic, 90 diastolic. The urine showed a ++ albumin, + red cells, + white cells, casts and specific gravity 1.008 to 1.012. The hemoglobin was 65 per cent, and the phenolsulfonphthalein excretion was less than 15 per cent in one hour. The nonprotein nitrogen was 121 mg., the serum calcium 8.2 mg., the serum phosphorus 9.8 mg. and the serum alkaline phosphatase 9.4 Bodansky units per 100 cc. The serum sodium was 107 milliequiv., the serum chloride 106 milliequiv. and the serum carbon-dioxide content 11.6 milliequiv. per liter. Roentgenograms showed calcium deposits in the soft tissues around the joints, the "moth-eaten" skull of osteitis fibrosa generalisata and several herniations of the nuclei pulposi of the vertebras. Autopsy showed stationary, if not healed, chronic glomerular nephritis, four much enlarged parathyroid glands, osteitis fibrosa generalisata and calcium deposits around the joints.

There are a few points that require some discussion. The edema would have been most unusual in primary hyperparathyroidism and is more consistent with chronic nephritis. Polyuria fits both conditions. The gastric ulcer is of some interest, in view of the frequency with which duodenal ulcers occur in primary hyperparathyroidism. The low serum-calcium level, though theoretically possible in primary hyperparathyroidism with secondary renal disease, is seldom seen in that condition; this favors primary renal disease. The deposits of calcium around the joints and in the olecranon bursa are more consistent with primary renal disease than with primary hyperparathyroidism.

I should like to look at the x-ray films.

Dr. James J. McCort: X-ray examination of the skull shows a diffuse demineralization of the bone, with small scattered islands of bone showing normal density. Both the inner and outer tables are thin, but there is no expansion of the diploë and no evidence of bone erosion or destruction. An examination of the teeth gave no information about the lamina dura because the patient is completely edentulous. There is demineralization of the mandible.

The chest films show a slight degree of emphysema, extensive calcification of the tracheal rings and marked calcification in the wall of the thoracic aorta. The lungs are entirely clear. A barium-swallow examination performed at the time the chest was examined shows a smooth soft-tissue indentation on the left lateral margin of the cervical portion of the esophagus. The esophagus at this level is displaced slightly to the right and is slightly narrowed.

Dr. Albright: It is not a single adenoma?

Dr. McCort: In our experience, displacement and compression of the cervical esophagus have been more common in the presence of parathyroid adenoma than with simple hyperplasia.

On the plain film of the abdomen are seen a few nodular calcific densities overlaying both kidneys.

Dr. Albright: Are there any stones?

Dr. McCort: These calcifications overlaying the kidneys seem most likely to represent renal calculi. Unfortunately, we do not have a pyelogram.

The bones of the lumbosacral spine and pelvis likewise show a diffuse demineralization, with thinning of the cortex and coarsening of the trabecular pattern. Incidental note is made of marked calcification of the abdominal aorta and pelvic vessels. A large number of small oval calculi are seen in the prostate. In the soft tissues adjacent to the ischial tuberosities, fleck-like deposits of amorphous calcification are seen. The examination of the long bones also discloses a diffuse demineralization. There are extensive vascular calcification and a few irregular deposits of calcium in the soft tissues. The femurs disclosed zones of subperiosteal bone absorption. The films of the hands and feet likewise show demineralization. In the distal phalanges, dissolution of the bone is noted in the midshaft. Fractures have occurred at the site of the dissolution of the bones; this accounts for the so-called clubbing of the fingers.

Dr. Albright: The clubbing of the fingers is due to fractures of the midshafts of the terminal phalanges with telescoping of the soft tissue. Identical clubbing was shown in roentgenograms taken on Captain Charles Martel, whose case played such a large part in the history of hyperparathyroidism.

My final diagnoses, then, would be chronic glomerulonephritis, osteitis fibrosa generalisata, secondary hyperparathyroidism in the four glands, arteriosclerotic heart disease with bundle-branch block, Mönckeberg's arteriosclerosis, ectopic calcification and calcification of the prostate.

One question I should raise is: Why operate? If this turned out to be a single adenoma I shall be very much surprised.

DR. BENJAMIN CASTLEMAN: Dr. Henneman, would you tell us why the patient was operated on?

DR. PHILIP H. HENNEMAN: Without the apparent mass in the neck displacing the esophagus by x-ray examination, this would have been a clear-cut case of primary renal disease with secondary osteitis fibrosa generalisata. However, the paraesophageal mass suggested the possibility of a parathyroid tumor in this region.

Primary hyperparathyroidism is most commonly characterized by an elevated serum calcium and a decreased serum inorganic phosphorus. Occasionally one encounters patients with primary hyperparathyroidism and decreased renal function due to nephrocalcinosis of renal calculi. These patients may have normal or even elevated serum-phosphorus levels associated with only minimal elevation of the serum calcium. The limiting degree of this latter situation appears to be a serum phosphorus sufficiently elevated to depress the serum calcium to levels lower than normal. I have never seen such a case, but I suspect it must exist.

We believed, despite the low serum calcium and elevated serum phosphorus, that the combination of a mass in the neck, osteitis fibrosa generalisata and renal calcinosis made it worth while to ask Dr. Raker to explore the patient's neck in the hope of finding a primary, — and causative, — parathyroid adenoma. Furthermore, we knew that removal of such a tumor in similar patients has been followed by arrest of the otherwise progressive renal disease — and even by improvement of renal function in some cases.

CLINICAL DIAGNOSIS

?Parathyroid adenoma.

DR. ALBRIGHT'S DIAGNOSES

Chronic glomerulonephritis.
Osteitis fibrosa generalisata.
Secondary hyperparathyroidism.
Ectopic calcification.

ANATOMICAL DIAGNOSIS

Parathyroid adenoma (and chronic renal disease).

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Dr. Raker, will you tell us about the operation?

DR. JOHN W. RAKER: We explored the left side of the neck first, expecting to see a tumor in the region of the x-ray shadow; we found behind the esophagus, wedged between the vertebral bodies and the thyroid gland, a tumor mass that we thought was consistent with a parathyroid adenoma. This was removed, and the pathologist, after seeing a frozen section, said it was probably a parathyroid adenoma. We explored the lower pole on this side and looked for an atrophic gland or another enlarged gland but did not find it. At this point the patient was not in good condition, so we desisted without exploring the right side of the neck. He had a great deal of difficulty postoperatively; he had what was probably a Stokes–Adams attack.

DR. CASTLEMAN: We studied this slide for a number of days to decide whether it was a primary adenoma or a secondary hyperplasia. Most of the cells were not enlarged and we could not find a capsule or at least a rim of normal tissue around the mass. However, we did find small fairly clear-cut acini, in contrast to the next slide, which is from the old case of definite secondary hyperplasia that Dr. Albright mentioned and which shows pseudoacini — cells surrounding small arterioles suggesting glandular arrangement. After studying many slides of the case under discussion, we found an area that proves to me that this was an adenoma — a group of cells varying in size, much bigger than normal. This variation in size, — at least in the material that we have, — is not seen in secondary hyperplasia, but it is the rule in adenomas. I believe, therefore, that this is probably a true adenoma rather than a secondary hyperplasia.

Dr. Henneman, will you discuss the follow-up on this patient?

DR. HENNEMAN: Before operation I believed that this patient had a parathyroid adenoma; after operation I was certain. However, the more I have thought about it the less certain I am that this was an adenoma and not secondary hyperplasia. Dreskin and Fox[3] have reported a similar case and found several others in the literature. Their patient had renal osteitis fibrosa associated with four hyperplastic glands, one of which was much larger than the others and was removed at an operation. It is of great interest that Dreskin and Fox's patient presented a fall in serum calcium and a rise in serum inorganic phosphorus after removal of the hyperplastic gland. Had these changes occurred in our patient I suspect we would have thought that this confirmed the etiologic status of the tumor. Actually, there has been little postoperative change in the pertinent blood chemical findings or clinical status of our patient. Finally, it seems to me that the lack of a rim of normal tissue around this mass is in favor of hyperplasia.

DR. CASTLEMAN: That is not necessarily the case. If a gland has enlarged enough as a result of a tumor, the rim is completely obliterated. As a matter of fact, in more than half of our cases we did not find a rim of normal parathyroid tissue. I have seen the material of two cases in which there was one very large parathyroid gland associated with primary renal disease, the other three glands being slightly enlarged and all showing secondary hyperplasia. I do not believe we have seen a large enough number of these cases to know whether we can tell

the difference between adenoma and secondary hyperplasia. The fact that the surgeon was unable to find the other gland on that side does not mean too much because the gland may have been in an aberrant location.

References

1. Albright, F., Drake, T. G., and Sulkowitch, H. W. Renal osteitis fibrosa cystica: report of case with discussion of metabolic aspects. *Bull. Johns Hopkins Hosp.* **60**:377-399, 1937.
2. Case Records of the Massachusetts General Hospital (Case 22072). *New Eng. J. Med.* **214**:320-325, 1936.
3. Dreskin, E. A. and Fox, T. A. Adult renal osteitis fibrosa with metastatic calcification and hyperplasia of one parathyroid gland: report of case. *Arch. Int. Med.* **86**:533-557. 1950.

CASE 38122

Presentation of Case

A forty-nine-year-old woman was admitted to the hospital because of upper-abdominal pain and vomiting.

Six months prior to entry the patient noted that she was losing weight and that she had become somewhat constipated, with bowel movements occurring only two to three times a week, whereas previously she had had a movement every day. Five weeks before admission she had the sudden onset of nausea followed by vomiting; the vomitus contained food eaten five hours previously. The following morning her temperature was 102°F. Shortly after this she began to have recurrent dull aching pain in the epigastrium that radiated into the left flank and the back. This was intermittent, lasted about an hour, was aggravated by solid foods and was relieved by hot milk and by sitting up and squeezing the abdomen. For the five weeks before admission her daily diet consisted of one quart of milk and a few crackers and cookies. On the two occasions on which she tried to take solid foods she vomited immediately and subsequently developed a brief elevation of temperature; altogether she had vomited four to five times during the five weeks prior to entry. Three days prior to admission for the first time she vomited after drinking milk.

There had been no hematemesis, dysphagia, jaundice or clay-colored stools. The constipation had become more marked and she had taken many laxatives; on a number of occasions in the four weeks prior to entry the stools had been black, but she had noted no fresh blood. She had had one-time nocturia for many years and an occasional attack of frequency and dysuria. She lost 12 pounds in weight in the five weeks prior to entry. There was no past history of anorexia, abdominal pain or vomiting.

Physical examination revealed a poorly nourished, dehydrated woman who appeared to be chronically ill. The mucosa of the tongue was smooth, red and atrophic. The lungs and heart were normal. There was tenderness to pressure in the epigastric region and in the left flank. A firm nontender liver was palpated 2 to 3 fingerbreadths below the costal margin. There was the suggestion of a firm, immobile, slightly tender orange-sized mass in the epigastrium. Pelvic and rectal examination was negative.

The temperature was 98°F., the pulse 72 and the respirations 18. The blood pressure was 140 systolic, 85 diastolic.

Examination of the blood revealed a hemoglobin of 12 gm., a red-cell count of 4,300,000 and a white-cell count of 7400, with 73 per cent neutrophils; a smear showed moderate hypochromia of the red cells. A urine of specific gravity 1.016 gave a ++ reaction for albumin; the sediment contained 15 white cells per high-power field. The nonprotein nitrogen was 24 mg., a fasting blood sugar 100 mg. and the total protein 6.5 gm. per 100 cc., with an albumin-globulin ratio of 1; the serum chloride was 100.3 milliequiv. and the carbon dioxide 25.3 milliequiv. per liter. The bilirubin was within normal limits. A stool guaiac test was negative. Roentgenograms of the chest showed slight enlargement of the left ventricle, tortuosity of the aorta and linear areas of atelectasis at the lung bases. A gastrointestinal series, barium-enema examination and Graham series were negative except for an indefinite ring shadow about and to the left of the duodenum. A film of the abdomen showed the right kidney to be low in position and slightly tilted. Overlaying the lower pole of the left kidney was a ring shadow of calcification. An intravenous pyelogram showed fair concentration of the dye by the right kidney; the calyces and pelvis of this kidney were grossly deformed and its lower pole was greatly enlarged, extending to the crest of the ilium and obliterating the psoas shadow. The dye was poorly excreted by the left kidney; a ring shadow overlaid the lower pole of this kidney. Retrograde pyelogram showed multiple pressure defects of the calyces of both kidneys; the defect of the lower pole of the right kidney was again demonstrated, and the ring shadow was seen to be in the region of the lowermost calyces of the left kidney (Fig. 1). The indigo-carmine appearance time was 4 minutes, with good concentration on both sides.

For the first two weeks in the hospital the patient had periodic attacks of sharp, continuous epigastric pain radiating to the back, that were followed by elevations of temperature as high as 104°F. There were no chills and no vomiting. The bowel movements were normal. Examination of the abdomen during these attacks revealed exquisite tenderness in the epigastrium without definite spasm and not affected by movements of the legs. Peristalsis was present. A white-cell count on the fifth day following one of these attacks was 12,400. Subsequent examinations between attacks failed to confirm the suggestion of an epigastric mass. After the second week she had periodic temperature elevations and vomited occasionally, but the epi-

gastric pain was not as marked a feature. An operation was performed on the twenty-fifth hospital day.

Differential Diagnosis

Dr. William C. Quinby, Jr.*: The history prior to admission in this case leads one inevitably to the speculation that the patient's primary disease was based in the gastrointestinal tract. In support of this statement were the evidence of progressive obstruction and the relation of the fever and pain to food. There was a question of melena; the vomiting of ingested solid food favors obstruction. The

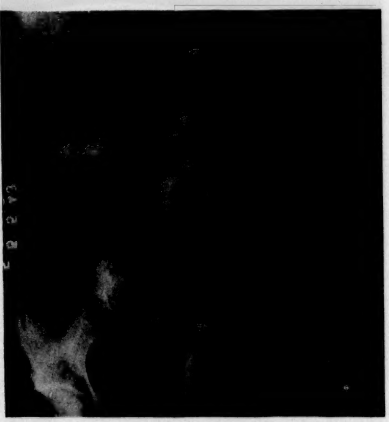


Figure 1.

position of the pain in the epigastrium that radiated to the back is also characteristic of a gastrointestinal disorder. The patient had a questionable epigastric mass, and initially her complaints were weight loss and progressive constipation. The physical findings, on examination in the hospital, were not very diagnostic, with the exception of the epigastric mass. The clinical laboratory findings were normal except for a ++ urinary albumin and 15 pus cells. The chemical laboratory examinations did not add anything. On hospital care, the obstructive elements of the complaints appeared to subside for two weeks at least. It is to be noted that the pain was not crampy in character, that the stools contained no blood when they were examined in the hospital and that she was apparently able to retain oral intake and have bowel movements normally.

To support the impression that the lumen of the gastrointestinal tract was not the primary site of the disease, the x-ray films are reported as showing no abnormality of the gastrointestinal tract. If the disease was not in the lumen of the gastrointestinal tract, could it have been associated with the pancreas or the biliary system? The pain was rather characteristic of pancreatic inflammation — epigastric, severe, going through to the back. The left-sided component of it is somewhat disturbing if I wish to incriminate the biliary tract; it is not exclusive. Ring-shaped shadows were seen in relation to the duodenum and to the lower pole of the left kidney. Tentatively, on the basis of the prior history, the hospital course and the laboratory findings, my first suspicion was that she had disease based in the pancreas. We do not have too important laboratory findings on the serum amylase and lipase determinations.

From x-ray films it appears that the major disease was related to the urinary tract; in this regard I shall ask Dr. McCort to help me.

Dr. James J. McCort: Examination of the intravenous pyelogram discloses that the patient has larger than normal kidneys. After the contrast substance was injected, excretion was seen to be slow. The calyces are elongated and spider-like. Retrograde studies confirm these findings. The calyces are spread apart to give the appearance of ice tongs (Fig. 1). No defects are seen in the ureter or bladder. A small ring-shaped calcification is seen over the lower pole of the left kidney. I think it is within the parenchyma of the kidney; its relation to the kidney is constant. No calcification is to be seen in the region of the pancreas.

The examination of the chest shows both leaves of the diaphragm to be high in position; the heart is prominent in the region of the left ventricle. There is a tortuous aorta. Plate-like areas of atelectasis are seen in both lung bases. The pulmonary vascular markings are slightly accentuated. Examination of the colon reveals a normal large bowel except for a slight downward displacement of the hepatic flexure by the liver. The examination of the upper gastrointestinal tract is entirely negative except for a suggestion of extrinsic pressure on the lesser-curvature side of the stomach. This is sometimes seen with enlargement of the left lobe of the liver.

Dr. Quinby: As the major demonstrable disease has shifted to the urinary tract, that would require me either to explain all the symptoms with regard to the urinary tract or to combine my gastrointestinal thesis with an additional finding, — and an extraneous one, — of multiple areas of destruction or infringement on the renal parenchyma. I am not a urologist, but I do know that bilateral disease of the kidney can produce the symptoms present here. In congenital polycystic kidney disease the symptoms most frequently shown are due to uremia, which this patient did not have, or to large palpable kidneys, which no one could feel in this thin woman. Bilateral malignant renal

*Assistant in surgery, Massachusetts General Hospital.

tumors are indeed a rare entity, whereas in progressive cystic degeneration of the kidneys the cysts, often being connected with the calyces or tubules of the kidney, occur bilaterally and can produce all this symptomatology. The fever element following meals, which is one of the predominant features of the clinical history, and the epigastric complaints with marked tenderness in that region lead me away from the basic findings of the x-ray films.

I would like to know whether or not the patient had a serum amylase determination.

DR. CASTLEMAN: None was done.

DR. QUINBY: I must take the known positive findings; thus in this case I shall say that the symptoms were on a renal basis. Fever frequently occurs with renal tumors, and the gastrointestinal symptoms may be entirely of reflex or secondary origin. There is evidence that she had had some urinary disturbance, with a history of frequency, and on admission she had albumin and pus cells in the urine. To relate it all to one finding, I should think this patient had cystic areas of degeneration in each kidney and that it was possible that on the left side also there was a malignant area in the kidney to which some of the more acute symptoms could be related. I do not believe she had typical polycystic disease of the kidney, and I cannot relate the symptoms, — except for some very gross spread of the carcinoma or something of that sort, — to the pancreas.

DR. WALTER ST. GOAR: I wonder if Dr. Quinby has any explanation for the large liver and the epigastric mass?

DR. QUINBY: I do not, Dr. St. Goar. The liver was mentioned once; the epigastric mass disappeared. The epigastric mass could have disappeared if pancreatitis had subsided, but I abandoned that diagnosis; I do not see how even that large a left kidney could present in the epigastrium.

DR. ALEXANDER LEAF: Polycystic disease involving the liver is known to occur together with renal involvement.

CLINICAL DIAGNOSIS

Congenital polycystic kidneys.

DR. QUINBY'S DIAGNOSIS

Cystic degeneration of the kidneys.
?Carcinoma of kidney, left.

ANATOMICAL DIAGNOSIS

Congenital polycystic kidneys and liver.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: This patient was operated on with a preoperative diagnosis of polycystic disease of the kidney; it was believed that the symptoms were due to the enlarging cysts. At operation many of the cysts were punctured and carbolized, and apparently the symptoms improved after that. At this time, therefore, the patient's symptoms were due to pressure from the polycystic kidney, but there was no evidence of renal insufficiency. The patient was well for seven years and then was readmitted in uremia with a nonprotein nitrogen of 250 mg. She was treated with the artificial kidney; the nonprotein nitrogen went down to under

FIGURE 2.

100 mg. at one time, and she was again well for almost two years. Then she finally died in uremia.

The autopsy showed these very large polycystic kidneys (Fig. 2), with a great deal of destruction of the parenchyma and, as Dr. Leaf suggested, the most marked polycystic liver (Fig. 3) that I believe I have ever seen.

A PHYSICIAN: In what percentage of cases of polycystic disease of the kidney does polycystic disease of the liver occur?

DR. CASTLEMAN: I cannot give you the exact percentages of cases in this hospital. One review of polycystic kidney disease cited an incidence of 33 per cent in 46 cases.

A PHYSICIAN: What was calcified within the kidney?

DR. CASTLEMAN: It probably resulted from old hemorrhage with organization and calcification.

By this time the patient died, nine years after her operation, she had developed hypertensive cardiac enlargement.

DR. JOHN B. STANBURY: What is the etiology of the cysts, and what is the relation between the cysts and the kidney?

DR. CASTLEMAN: In that connection Lambert[2, 3] has recently done some interesting work in Belgium. It has been known that a patient with this disease dies either in infancy or between the ages of forty-five and sixty, and there has been a great deal of discussion about the reason for that long hiatus. Lambert made models of the nephrons and showed that in the newborn all the cysts of either a glomerulus or a tubule are closed cavities. The reason these infants die is that everything is a closed system. In the adult, on the other hand, in his reconstructed models, he shows that these cysts are really diverticula of the tubules that as they enlarge gradually replace parenchyma. Contrary to the usually accepted theory that there is no connection between glomerulus and tubule, Lambert believed, and I think the evidence is pretty strong, that these kidneys do function and do not have a closed system. The old idea that there is a dissociation between the glomerular tuft and the tubular system is probably not correct.

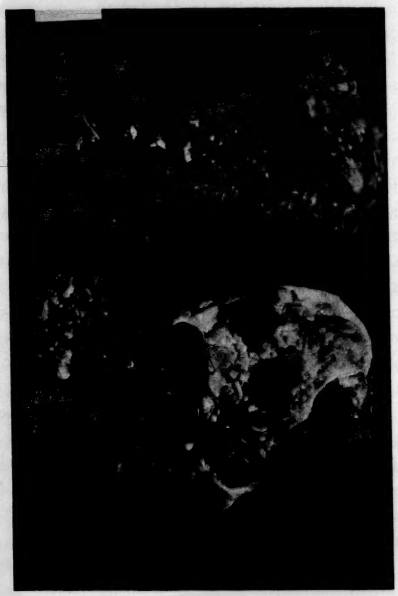


FIGURE 3.

DR. STANBURY: I was wondering about the liver.

DR. CASTLEMAN: We know that patients with polycystic kidneys are likely to have other congenital defects. In the liver these cysts are lined with bile-duct epithelium. In 1906, Moschcowitz[4] wrote a very interesting paper in which he stated that he believed that the cysts were congenital aberrant bile ducts that enlarged and compressed the surrounding liver tissue. I do not believe it is ever sufficiently extensive to cause liver insufficiency.

DR. WILLIAM CLARK: Dr. Bauer will remember a patient who died with jaundice and with evidence of liver insufficiency. I believe you have the specimen, Dr. Castleman.

DR. CASTLEMAN: That patient had a purulent hepatitis in addition to the cysts, which accounted for the slight jaundice. Occasionally these patients have pancreatic cysts also.

DR. WALTER BAUER: It is also reported that people with congenital cystic disease of the kidney have bicuspid aortic valves.

DR. CASTLEMAN: Almost any congenital anomaly may be seen in association with this condition.

A PHYSICIAN: Did you examine the brain of this patient?

DR. CASTLEMAN: Yes; apparently there was nothing abnormal.

A PHYSICIAN: A man named Berry found aneurysms, called Berry aneurysms, of the middle cerebral artery in patients with polycystic kidneys. Did you find any aneurysms?

DR. CASTLEMAN: No.

REFERENCES

1. Rall, J. E., and Odel, H. M. Congenital polycystic disease of kidney: review of literature and data on 207 cases. *Am. J. M. Sc.* **218**: 399-407, 1949.
2. Lambert, P. P. *Le rein polykystique. Étude morphologique, clinique et physiopathologique.* 140 pp. Paris: Masson & Cie, 1943.
3. Lambert, P. P. Polycystic disease of kidney: review. *Arch. Path.* **44**: 34-58, 1947.
4. Moschcowitz, E. Non-parasitic cysts (congenital) of liver, with study of aberrant bile ducts. *Am. J. M. Sc.* **131**:674-699, 1906.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY
OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. Richard E. Ait, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. Donald Munro, M.D.
Theodore H. Ingalls, M.D.

Clara D. Davies, EXECUTIVE EDITOR

Robert O'Leary, ASSISTANT EDITOR*

EDITORIAL BOARD
C. Guy Lane, M.D. Maxwell Finland, M.D.
Henry R. Viets, M.D. C. Stuart Welch, M.D.
Robert M. Green, M.D. Vernon P. Williams, M.D.
Dwight O'Hara, M.D. Benjamin Castleman, M.D.
Fletcher H. Colby, M.D. Hugh R. Leavell, M.D.
Robert L. Goodale, M.D. J. Englebert Dunphy, M.D.
Chester M. Jones, M.D. Robert W. Buck, M.D.
Harvey R. Morrison, M.D. Herrman L. Blumgart, M.D.
Deering G. Smith, M.D.†

*On leave of absence with the Armed Forces.
†Representing the New Hampshire Medical Society.

SUBSCRIPTION TERMS: $8.00 per year in advance, postage paid, for the United States (medical students and first-year interns, $5.00 per year); Canada, $9.00 per year (Boston funds); foreign, $10.50 per year.

MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

PROGRESS IN THE TREATMENT OF TUBERCULOSIS

THE Eleventh Conference on the Chemotherapy of Tuberculosis took place January 17–20 in St. Louis. The conference was attended primarily by workers who are devoting their major efforts to the treatment of tuberculosis in Veterans Administration Hospitals, in certain Army hospitals (notably Fitzsimons Army Hospital) and at some Navy installations. Among participants were a number of outstanding surgeons, who have had long and continuous interest and experience in the surgical aspects of tuberculosis. Also in attendance were a few invited guests who are well known for their contributions in the fields of tuberculosis and chemotherapy.

This conference, like its predecessors, was another landmark in the progress of tuberculosis therapy achieved through earnest co-operative efforts, under the intelligent and inspiring leadership of the Tuberculosis Division of the Veterans Administration's Department of Medicine and Surgery. As the title of the conference implies, its deliberations were largely devoted to a review of the results of treatment of pulmonary and other forms of tuberculosis with various dosage regimens and combinations of therapeutic agents. The participants also heard interesting and important original communications. Details of the deliberations of this conference will later be available through the publication and distribution of its transactions and through the publications of the individual contributors. It is hoped that, in addition, a concise summary of the more important facts brought out and of the conclusions reached during the course of the deliberations will also be made available for more general circulation. The summaries of previous conferences have proved most helpful to practitioners and to specialists in this field.

A few points on which there appeared to be general agreement among the conference's participants are worthy of note. These conclusions were based on objective analysis of various forms of treatment during the past few years in about 6000 cases that were documented and analyzed.

Unanimity of opinion was general concerning the currently preferred dosage regimen for the chemotherapy of pulmonary tuberculosis, namely, the so-called "intermittent-combined regimen," in which 1 gm. of streptomycin (SM) is given either every third day or twice a week and 12 gm. of para-aminosalicylic acid (PAS) is given daily. This dosage has been found to be clinically as effective as other regimens employing larger or more frequent doses of SM, provided that treatment is continued for four months or longer. That intermittent rather than daily SM dosage is to be preferred in respect to convenience, cost, patient acceptance, amount of nursing required and so forth is obvious. It was also clearly shown that this intermittent-combined regimen delays the emergence of streptomycin resistance of the tubercle bacilli and also considerably reduces the incidence and severity of toxic effects

of SM, thus permitting longer courses of administration.

It was the consensus that continuous and prolonged treatment is, in the long run, better than shorter or repeated courses of treatment. The optimum duration is yet to be determined, but it was believed that it should be definitely longer than was previously believed and that it should certainly be more than four months. It was also generally agreed that retreatment of cases of pulmonary tuberculosis, even when the tubercle bacilli in the sputum are still sensitive to both SM and PAS, gives distinctly poorer end results than do initial courses of treatment begun in comparable cases and carried out for the same length of time. This puts further emphasis on prolonged chemotherapy in the initial course of treatment.

Dihydrostreptomycin and streptomycin, when used in similar doses, apparently gave similar results with respect to toxicity and to the over-all effect on the course of tuberculous infection. It was thought, however, that more extensive and carefully controlled studies in parallel series of cases are still needed in order to determine any real differences in the effects of these agents. An account of such a controlled study currently in progress was announced, but the results are not yet available. Another feature of tuberculosis treatment that needs careful, prolonged and controlled study is the need or value of various types of rest and general supportive measures, particularly in relation to chemotherapy.

One of the more exciting discussions concerned the evaluation and possible implications of the results of recent types of conservative pulmonary resection carried out during or after prolonged chemotherapy. In certain carefully selected cases, the results of "wedge" or segmental resections of residual necrotic lesions carried out during or immediately after prolonged chemotherapy indicated that these lesions may contain many easily visible organisms. Such organisms, however, have proved to be nonviable in these cases by any known cultural technic or by inoculation of susceptible animals. This suggests the possibility that a genuine cure, with complete eradication of tuberculous disease, might be in prospect for some cases.

Gratifying progress has also been achieved in the treatment of miliary and meningeal tuberculosis. On the basis of a significant number of cases treated and followed for from one to two years, it is now clear that the combination of streptomycin and para-aminosalicylic acid used continuously for long periods has increased the recovery rate in cases of miliary and meningeal tuberculosis. The increase in the survival rates over those obtained through continuous treatment of similar cases with streptomycin alone was significantly high.

Several interesting reports described important pilot studies in which new or promising anti-tuberculosis agents were used or new or radical departures in dosage forms were studied. The results of such studies were, obviously, only suggestive. However, it can be said unequivocally that no important competitor of streptomycin was revealed through these studies. Neomycin, although apparently promising on the basis of *in-vitro* studies, has proved to be entirely too toxic for extended use; it might conceivably be tried in truly desperate circumstances, as, for example, in streptomycin-resistant cases of meningeal tuberculosis.

Preliminary explorations of another antibiotic, viomycin, suggest that this is an effective anti-tuberculosis agent. It was found definitely inferior to streptomycin in its anti-tuberculosis activities and also of much greater toxic potentiality. Its use requires careful control of electrolyte balance. For these reasons it was not found useful as a short-term chemotherapeutic agent in conjunction with surgical procedures. However, its potentialities when used either alone or in combination with other agents, particularly in streptomycin-resistant cases, appeared worthy of further exploration.

Terramycin, when well tolerated, was found to be useful as a substitute for PAS and gave essentially similar results in enhancing the effect of streptomycin and delaying the emergence of streptomycin-resistant tubercle bacilli. On the other hand, thiosemicarbazone (TB1), which had previously been found highly toxic in effective dosage, was shown to be less valuable in nontoxic doses; it was therefore thought that this drug would not find a place in the armamentarium of the phthisiologists.

A new simple chemical, pyrazinamide (Aldinamide), which is related to niacin, was revealed as much more effective than PAS against tuberculous infections of animals. In preliminary clinical trials the immediate or early effects of this agent in the treatment of pulmonary tuberculosis due to either streptomycin-sensitive or streptomycin-resistant organisms seemed impressive, and its toxicity was low. Unfortunately, tubercle bacilli apparently developed resistance to this agent with unusual rapidity. Further studies of possible methods of avoiding this phenomenon while preserving its anti-tuberculosis activity are obviously indicated and are already in progress in several hospitals.

It was indicated at the time of this conference that Aldinamide is only one of a group of closely related anti-tuberculosis compounds, several of which were already under study by the same and other groups of workers. About a month later one such compound, the hydrazide of isonicotinic acid, received widespread publicity in the public press and via radio. Much remains to be learned about the usefulness and limitations of these new drugs.

MONEY TALKS

DESPITE its expressed disapproval of a multiplicity of fund-raising campaigns striving competitively for the buck that is becoming not so easy to procure, the *Journal* nevertheless recognizes the validity of the claims of most of these charities and wishes them success in their efforts to remodel mankind somewhat nearer to the heart's desire.

The March of Dimes, the American Heart Association, the American Cancer Society, the National Society for Crippled Children and Adults, the American Red Cross and others, most of which have recently held or are about to launch their campaigns for money, may not all consider themselves charitable institutions, but the word is used in its broadest and most charitable sense.

For charity, of which the now rare definition "divine love for man" may still be preferred by many, is that which suffereth long and is kind, which envieth not, which vaunteth not itself and is not puffed up.

The reckless extravagance of government, from its lowest to its highest levels; the profligacy of so many officials occupying positions once considered public trusts; the corruption and the professional crime that exist on a scale hitherto undreamed of — all divert into rapacious hands the wealth that could mean so much to mankind if properly used. These factors, combined with private selfishness, are the reason that so many organizations have considered it necessary to desert the various community chests, which represent the basic needs of their localities, and to introduce a factor of competition that is foreign to their fundamental principles. Money talks, but in such varied tongues!

One is reminded again of Paul's First Epistle to the Corinthians:

> *But God hath chosen the foolish things of the world to confound the wise; and God hath chosen the weak things of the world to confound the things which are mighty.*

AID FOR THE DISABLED

A NEW state law, which went into effect on November 1, 1951, by the enactment of Chapter 741 of the Acts of 1951, adds a new class to the previously existing categories of persons entitled to public assistance. By the passage of this act, which has now become Chapter 118D of the General Laws of Massachusetts, a program of disability assistance to be administered by local boards of public welfare is devised to provide "assistance to needy persons, eighteen years of age or over, who are permanently and totally disabled."

Under this law a permanently and totally disabled person is defined as one with "a major physical or mental disease or loss that substantially precludes him from engaging in a useful occupation within his competence, such as holding a job or homemaking." The assistance guaranteed is to be financed by Federal, state and local governments and, largely because of federal participation, since the requirements of the Social Security Act and the Federal Security Agency must be met, the permanence and degree of the disability are to be established in each case.

The qualifications for aid must be based on the findings of a physician; consequently the co-operation of the medical profession in Massachusetts is necessary. Furthermore, in order that the requirements of the Federal Security Agency may be met,

the State Department of Public Welfare has been required to establish a medical review team to scrutinize each medical report and determine its eligibility.

Each extension of those activities of government that are intended to broaden social and economic security constitutes a step in the direction of increased paternalism. Such activities also have their benefits, often needed and of a humanitarian nature, to various segments of society. They also entail increased dependence of certain parts of society on other parts that are still willing and able to bear the burden. For the benefits that even government has to bestow must come from the sweat of some persons' brows.

Aid for the totally disabled appears to be a wise provision on the part of government. In the hands of the medical profession is placed part of the responsibility for seeing that this aid is wisely and justly administered.

A MYTH EXPLODED

THE unfortunate proclivity of the statisticians of the Metropolitan Life Insurance Company for quoting statistics seems to have exploded what they now characterize as another myth. This is the commonly held belief that marriages increase in leap year, of which 1952 is one. The release, having been issued in January, obviously concerns 1952 only by inference.

The chances of emboldened woman's taking the advantage of reluctant man are particularly poor for 1952, according to the statisticians, because the supply of available unmarried persons of both sexes has run out, due to the increased marriage rate after the close of World War II.

Figures, properly treated, do not lie, and it appears that only twice since the Civil War, in 1896 and in 1920, has a leap-year marriage rate exceeded that of the years immediately preceding and following it. The fact seems thus to be incontrovertibly established that during leap year man courteously abandons his customary role of the pursuer, in order to give to the weaker sex an advantage that its members do not wish to take.

There is no reason why gentlemen should irritate each other with personal abuse, because they happen to differ in opinion upon any subject. Literary and scientific men achieve for themselves distinguished honor when they reason with each other in courteous language.

Boston M. & S. J., *March 24, 1852*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BARRON — Elmer W. Barron, M.D., of North Hanover, died on January 20. He was in his seventy-sixth year.

Dr. Barron received his degree from Harvard Medical School in 1903. He was professor of pediatrics, emeritus, at Tufts College Medical School, a former president of the New England Academy of Pediatricians, a fellow of the American Medical Association and a member of the American Academy of Pediatricians.

His widow and three children survive.

CASEY — John F. Casey, M.D., of Allston, died on March 5. He was in his sixty-seventh year.

Dr. Casey received his degree from Columbia University College of Physicians and Surgeons in 1909. He was a fellow of the American Medical Association, a councilor of the Massachusetts Medical Society and a former president of Middlesex South District Medical Society.

His widow, five sons and two daughters survive.

CLARKE — Harry C. Clarke, M.D., of Lynn, died on February 21. He was in his seventy-fourth year.

Dr. Clarke received his degree from Harvard Medical School in 1910. He was a member of the Lynn Medical Fraternity and a fellow of the American Medical Association.

His widow survives.

GRAY — George H. Gray, M.D., of Hyannis, died on February 19. He was in his eighty-ninth year.

Dr. Gray received his degree from the University of Vermont College of Medicine in 1888. He was a member of the American College of Surgeons and the New England Surgical Society, and a former president of the Lynn Medical Fraternity, the Essex County Medical Society and the Barnstable District Medical Society.

His widow and a sister survive.

LEE — Joshua M. Lee, M.D., of Denver, Colorado, died on November 30, 1951. He was in his sixty-second year.

Dr. Lee received his degree from Boston University School of Medicine in 1923.

His widow survives.

MONAHAN — John A. Monahan, M.D., of Clinton, died on February 21. He was in his seventy-fourth year.

Dr. Monahan received his degree from Tufts College Medical School in 1902. He was a member of the American Academy of Ophthalmology and Laryngology and a fellow of the American Medical Association.

A brother survives.

PARKER — Willard S. Parker, M.D., of Cambridge, died on February 18. He was in his seventieth year.

Dr. Parker received his degree from Harvard Medical School in 1909.

Two daughters survive.

REILLY — Thomas E. Reilly, M.D., of Marlboro, died on February 27. He was in his sixty-eighth year.

Dr. Reilly received his degree from Dartmouth Medical School in 1910. He was a fellow of the American Medical Association.

His widow and two sons survive.

BOSTON MEDICAL LIBRARY

BOSTON MEDICAL LIBRARY NOTE

Harofé Haivri, the Hebrew medical journal (**2**: 92-124, 1951), presents three articles of historical importance: "Jewish Contributions to the Development of Medical Psychology," by Henry R. Gold, M.D.; "Persian Medicine and Its Relation to Jewish and Other Medical Science," by Zussmann Muntner, M.D.; and "Zacutos Lusitanus," by Y. Leibovitz, M.D. The Hyams collection of Judaica and Hebraica and the Bullard collection of incunabula, all in the Boston Medical Library, are rich in the authors mentioned — Philo Judaeus, Moses Maimonides, Rhazes, Haly Abbas, Avicenna and Zacutos Lusitanus. The Avicenna collection is notable for its many early manuscripts written in Arabic, Hebrew, Spanish and Latin; it contains 10 incunabula, including the first medical book printed in Hebrew, the complete *Canon medicinae* (Naples, 1491).

CONAN DOYLE AND SHERLOCK HOLMES

The famous stories of Conan Doyle (a physician) about the adventures of Sherlock Holmes have been translated into Icelandic and published in five octavo volumes at Reykjavik (1945–1949). Likewise, a number of single items of Doyle have been issued from Iceland in the native language. The Library has added twenty-two of these titles, in addition to the set mentioned above, to its large Doyle collection.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

TYPHOID EPIDEMIOLOGY

Painstaking follow-up of clues in epidemiologic studies of typhoid fever is often rewarded by the successful elucidation of the source of a case or an outbreak, but when the pointers are few, as occurred recently in the Worcester area, disappointments are often just as frequent.

Two cases of typhoid fever, occurring within the same month in adjacent towns, proved to be due to the same phage type of organism and were probably connected. Thorough history taking and follow-up of clues led the investigator to a large food store. Through the co-operation of the management, a questionnaire and a stool culture were obtained from each employee but revealed nothing. One employee was suspected, on the basis of his personal history, but repeat cultures on this person did not confirm the suspicion.

Other phases of the investigation included examination of a dairy and its employees, one other food store and the family connections in both cases. Of known carriers in the area, one harbors the same phage type of organism, but there was not even a remote contact between this person and the patients. This carrier was responsible for an illness in a member of his own family, however — a person who had failed to report for her periodic booster doses of typhoid vaccine. She said that she had done this on the advice of a physician. That vaccination of family contacts of typhoid carriers should be kept up to date need hardly be stressed to family physicians.

A third case in this area may yet lead to the unsuspected and unsuspecting carrier who was responsible for the cases recorded above.

KENNETH I. E. MACLEOD, M.D.
District Health Officer

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JANUARY, 1952

RÉSUMÉ

DISEASE	JANUARY 1952	JANUARY 1951	SEVEN-YEAR MEDIAN
Chancroid	4	4	3
Chicken pox	1866	2633	2322
Diphtheria	5	15	18
Dog bite	644	790	579
Dysentery, bacillary	0	3	10
German measles	783	98	98
Gonorrhea	182	238	266
Granuloma inguinale	0	1	0
Lymphogranuloma venereum	2	1	1
Malaria	0	0	1
Measles	9565	840	1018
Meningitis, meningococcal	8	7	7
Meningitis, Pfeiffer bacilius	6	11	4
Meningitis, pneumococcal	4	1	4
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	7	3	5
Mumps	1889	1666	1517
Poliomyelitis	2	8	1
Salmonellosis	3	6	4
Scarlet fever	350	714	714
Syphilis	292	147	212
Tuberculosis, pulmonary	193	207	213
Tuberculosis, other forms	16	10	12
Typhoid fever	0	0	0
Undulant fever	1	1	2
Whooping cough	382	408	480

COMMENT

The only disease markedly above the median was measles. The increase began in December and was accelerated in January. This may either indicate an early peak for the season or signal a high measles year. The disease was widespread in distribution, involving most populous centers. Immune globulin must be used wisely or the supply will not last for the season.

The diseases slightly above the median are German measles and mumps.

The diseases below the median are chicken pox, diphtheria, scarlet fever and whooping cough, diphtheria reaching the lowest level ever recorded for the month.

Scarlet fever dropped to the lowest level ever recorded for January.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES
January, 1952

Anthrax was reported from: Lynn, 1.

Diphtheria was reported from: Boston, 1; Cambridge, 2; New Bedford, 1; West Springfield, 1; total, 5.

Encephalitis, infectious, was reported from: Chicopee, 1; Dedham, 1; Framingham, 1; Haverhill, 1; Leominster, 1; Shrewsbury, 1; Wakefield, 1; West Springfield, 1; total, 8.

Hepatitis, infectious, was reported from: Boston, 1; Brookline, 1; Cambridge, 1; Greenfield, 2; Medford, 3; Worcester, 2; total, 10.

Meningitis, meningococcal, was reported from: Arlington, 1; Billerica, 1; Cambridge, 1; Fall River, 1; New Bedford, 1; Wakefield, 1; Winthrop, 1; Worcester, 1; total, 8.

Meningitis, Pfeiffer-bacillus, was reported from: Braintree, 1; Chelsea, 1; Melrose, 1; Needham, 1; Quincy, 1; Weymouth, 1; total, 6.

Meningitis, pneumococcal, was reported from: Belmont, 1; Bourne, 1; Pittsfield, 1; Swansea, 1; total, 4.

Meningitis, mumps, was reported from: Malden, 1; Sharon, 1; total, 2.

Meningitis, undetermined, was reported from: Adams, 1; Chelsea, 1; Malden, 2; Medford, 1; Springfield, 1; Worcester, 1; total, 7.

Poliomyelitis was reported from: Clinton, 1; Springfield, 1; total, 2.

Salmonellosis was reported from: Haverhill, 1; Medford, 1; Worcester, 1; total, 3.

Septic sore throat was reported from: Adams, 1; Boston, 2; Greenfield, 2; Warren, 1; Westford, 1; Worcester, 4; total, 11.

Tetanus was reported from: Brockton, 1; Weymouth, 1; total, 2.

Trichinosis was reported from: Boston, 1.

Undulant fever was reported from: Lowell, 1.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The April schedule for Consultation Clinics for Crippled Children in Massachusetts follows:

Orthopedic Clinics	Date	Clinic Consultant
Haverhill	April 2	William T. Green
Greenfield	April 3	Charles L. Sturdevant
Lowell	April 4	Albert H. Brewster
Salem	April 7	Paul W. Hugenberger
Gardner	April 8	Carter R. Rowe
Brockton	April 10	George W. Van Gorder
Lynn*	April 14	Daniel M. Killoran; John J. Crowley
Springfield	April 15	Garry deN. Hough, Jr.
Pittsfield	April 16	Edward J. Coughlin, Jr.
Hyannis	April 17	Paul L. Norton
Worcester	April 18	John W. O'Meara
Fall River	April 28	David S. Grice

Rheumatic-Fever Clinics	Dates
North Reading	April 1, 8, 15, 22, 29
Fitchburg	April 2, 9, 16, 23, 30

Plastic Clinics	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon
Western Massachusetts	Monthly	Joseph M. Baker

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Hospital.

CORRESPONDENCE

AN ANALYSIS OF THE UNION HEALTH-DEPARTMENT LAW

To the Editor: In 1950 the Town of Marion appointed a Moderators Committee to study the Union Board of Health Law (Chapter 662 of Acts of 1949). This committee has been active and has furnished speakers for various organizations in the Fourth Plymouth District, who in turn have sponsored Moderators Committees to be appointed at the next town meeting in their respective localities.

We have endeavored to present an explanation to the taxpayers of the power of this law, which is primarily a bureaucratic piece of legislation that if accepted as written by all towns and municipalities with a population under 35,000 will put another sizable assessment per capita on the taxpayer. Finance boards and planning boards have been advised that this assessment is in addition to the usual health appropriations made by various towns for tuberculosis hospitals, sewage disposal, cemeteries, dumps and so forth. School boards have been contacted and the law, as related to school health programs, has been analyzed for them.

This is the type of legislation that all of us in our lifetime will have to accept as a surrender of the powers of local health agencies to the Department of Public Health or else consolidate with other towns and work out some modification that fits our needs and our pocketbooks. This is government medicine, and no mistake should be made about that.

All medical men who practice in towns should take the trouble to write their district health officers for copies of this law and also for the minimum requirements defined by the Public Health Council.

There is a provision in the law that if these various towns form their own union board they may be exempt from some of the top-heavy requirements of the table of organization as defined in the law. The law is comprehensive in all matters pertaining to public health and is mandatory in that it specifically states that if these towns do not either join or form a satisfactory board by 1959 they will be assigned, after a hearing, to a Union Board by the State Department.

Whether these towns accept the law as is or establish their own boards, they *must*, through the local boards of health, provide a central laboratory. There is no appropriation by the State Department or Federal Government that will cover the cost of such a laboratory and its maintenance before the formation of some sort of board. The State Department has no plans that can be ascertained for buying costly laboratory equipment, and it is evident that this burden will have to be assumed by the taxpayer.

The minimum requirements defined by the State Department are designed to give employment under Civil Service (except the director of health) to a supervising sanitary officer; a sanitarian per 25,000 population; a supervising nurse and sufficient nurses with public-health training to make up quotas for each area; a senior-grade clerk and one clerk; stenographer per 15,000 population.

The director of health will be in charge of all these agencies and he may appoint deputies as he sees fit to carry out his directives. This is in addition to the cadre of State workers who without any examination automatically become civil-service employees with all the privileges, under the law, of pension rights, and so forth. This director may be removed after five years by the vote of the representatives appointed by each town, who serve at no pay on the Union Board — that is, he may be removed if the State Department approves. Once they occupy these respective offices under Civil Service, the remote possibility of unloading any of them will prove to be a problem for all towns concerned.

The minimum requirements control: communicable diseases; analysis of water, milk and milk products; foods and their processing, storage, handling and transportation; swimming pools; bathing and recreation areas; summer camps; the sanitary aspects of tourist homes and cabins, rooming houses, day nurseries and hospitals; nursing, convalescent and boarding homes; health aspects of housing; sanitation in schools; animal inspections and slaughterhouses; noisome trades; private sewage disposal and private water supplies; and programs for insect and rodent control.

Maternal and child health, from pregnancy through school years, with establishment of conferences and clinics and home visits by public-health nurses, are included with all their ramifications in the requirements. The premature-infant agency will also come under this division. School-health programs, where they are not provided, will be controlled by the board.

Health-education and social-welfare departments will give guidance to physicians and lay groups in solving personal and public-health problems through conferences and lectures. Films, news stories, posters, annual reports, exhibits and pamphlets will be provided by this division.

Vital statistics will be analyzed and applied to community health problems.

The board will supervise civil-defense health problems.

Boards of health may be delegated certain duties, but the wording of the law is not specific, and it may well be that they will be stripped of power unless it coincides with the will of the State Department.

This legislation stems from the State Department. The Governor and Executive Council are not mentioned in the Act. We have no disagreement with the concept of this law and are cognizant that there are areas in the Commonwealth without efficient boards of health or health agencies, but to take over the powers of town government and to try to apply it by force to areas like our own seems, despite the assurance of the Commissioner that the Department wants it done "on the local level," dangerous legislation. A law is a law, and there are many "shalls" and "musts" embodied in the wording of this Act. There is bound to be overlapping with other agencies — and this law applies *only* to small towns and municipalities. Where the district health officers fit in this set-up is answered easily; they do not. In our particular area we have been well covered by the district officer in our homes and hospitals and we are thankful that we have this service. Now we are commanded to scrap him and be guided by the director of health.

All employees concerned in this new organization will be trained high-grade persons (we hope) who are not planning to work for small salaries. It is easy to predict a large payroll to be met by pro-rata assessments by the Union Board, to be paid by member towns. No one can be so naïve as not to see the political possibilities in the power of a director to appoint deputies with civil-service protection. It could become a permanent load on small communities, and it seems to this committee that the only feasible plan is to organize now and to work out some compromise with the Department. It is a costly and revolutionary law — one that pertains not only to health problems but also to the infiltration by government into schools, homes and business.

RAYMOND H. BAXTER, M.D., *Chairman*
Marion, Massachusetts

ACTH IN EYE DISEASE

To the Editors: In their review of ACTH and cortisone in treatment of ocular disease, which recently appeared in the *New England Journal*, Smith and Steffensen misquoted results reported by us at the Second Clinical ACTH Conference and, in so doing, have tended to obscure the great therapeutic value of long-acting ACTH preparations in eye disease. The reviewers incorrectly state that we reported "the dosage (of long-acting ACTH) often dangerously high and the therapy impractical." The report made at the Second Clinical ACTH Conference, however, was distinctly optimistic in tenor.

Actually, in the disorders studied, the results obtained with long-acting ACTH treatment have been appreciably superior to those previously reported by any other group, with respect to both immediate and long-term results. Our studies have been confined to syndromes that previous workers had reported to respond irregularly or transiently to ACTH or cortisone. The 33 patients treated included cases of chronic disseminated chorioretinitis(7), chronic central angiospastic retinopathy(2), chronic retrobulbar neuropathy due to multiple sclerosis and that due to syphilis(2), other chronic inflammatory retinal disorders (3), acute optic neuritis (4), acute retrobulbar neuritis (6), acute disseminated chorioretinitis (2), chronic anterior-segment inflammatory disorders refractory to topical cortisone ointment(3), and acute recurrent iridocyclitis refractory to topical cortisone ointment(4).

In 88 per cent (29 of 33 patients), normal or useful vision was restored. No patient has relapsed from his maximum improvement*, although a few patients require some maintenance hormonal treatment if they are to hold their full improvement. In this series, a deliberate effort was made to treat patients whose ocular status appeared to give them a particularly unfavorable prognosis. However, apart from this selection, we treated all patients whose condition appeared to warrant therapy irrespective of any contraindication to ACTH treatment other than tuberculosis. Despite this nonselection of patients, and despite the necessity of using unconventionally large ACTH dosages to achieve these results, hypercorticoid manifestations were far less frequent and less serious than during the hormonal treatment of systemic illnesses such as rheumatoid arthritis. Unfavorable side-effects necessitated the cessation of treatment in only 4 patients; in 3 of these the side-effect noted was heightening of a neurotic anxiety that had been recognized before therapy was begun. In addition, since administration of long-acting ACTH does not ordinarily require hospitalization, the actual cost of such treatment to the patient may be considerably less than that of continuous infusions or intermittent intramuscular injections of ACTH, both of which ordinarily require hospitalization. From the foregoing, it is apparent that we have found the use of long-acting ACTH preparations neither dangerous nor impractical in this serious group of eye diseases.

Furthermore, our experience does not agree with Smith and Steffensen's impression that "by the third week of parenteral therapy further regression of the lesion is usually slow and, in view of the possible pharmacologic effects, continuation of the intensive therapy does not appear justified." Several patients treated with long-acting ACTH have presented long-standing, apparently inactive, severe lesions of the retina or optic nerve that have failed to show significant improvement for the first thirty to seventy-five days of hormonal therapy and that subsequently have improved to the point where normal or useful vision was restored. Such improvement, which begins only after prolonged treatment, has not been seen in other than eye disease, to the best of our knowledge, and it appears to represent a new type of therapeutic response to adrenal cortical hormones.

A detailed report of our findings will appear elsewhere in the near future.†

WILLIAM Q. WOLFSON, M.D.
JAMES R. QUINN, M.D.
Ann Arbor, Michigan

*Criteria for the restoration of useful vision include distance acuity of 20/50 or better, reading vision of Jaeger 4 or better, no central scotoma to 2/1000 white object, minimal flare and no cells in the anterior chamber and minimal evidence of irritation of periocular structures.

†Quinn, J. R., and Wolfson, W. Q. Improved results from individualized intensive hormonal treatment of certain eye diseases which have been reported to respond poorly to ACTH or cortisone. *University of Michigan Medical Bulletin*, January, 1952 (in press).

The letter of Drs. Wolfson and Quinn was submitted to Drs. Smith and Steffensen, who offer the following reply:

Doctors Wolfson and Quinn have called attention to certain misinterpretations by us of results that Dr. Wolfson and others had reported previously at the Second Clinical ACTH Conference. We sincerely regret this unintentional literary mishap and agree that the over-all tenor of the concerned report was, as they write, "distinctly optimistic."

The particular passage that "tended to obscure" the nature of Dr. Wolfson's report and that is quoted in the opening paragraph of their letter is part of a sentence concerning the treatment of *chronic* inflammatory eye lesions with long-acting ACTH preparations. Dr. Wolfson had reported at the Second Clinical ACTH Conference that control of recurrent chorioretinitis required an average of 157 mg. per day and that discontinuation of treatment without relapse of such lesions had not been achieved. Of 4 such cases, 2 "showed relatively minor improvement except at dangerously high doses and continuation of treatment was deemed impractical." We certainly agree that our use of the word "often" was misleading.

In regard to Paragraph 4 of their letter, we express our disappointment that we were not quoted a little more at length to include the succeeding statement that "exceptions to this therapeutic program will be encountered, and individualization of case therapy may often be necessary for optimum results." This might be applied to the "several patients" of which Drs. Wolfson and Quinn write as having shown recovery of useful vision.

Finally, in respect to the principal portion of their letter, we express our pleasure in having read the results that Drs. Quinn and Wolfson have achieved recently. We are pleased that their work, heretofore unpublished, will appear soon for proper recognition in future reviews.

RICHMOND W. SMITH, JR., M.D.
ELLIS H. STEFFENSEN, M.D.
Detroit, Michigan

NECESSITY FOR ADEQUATE INSULIN DOSAGE

To the Editor: In rebuttal to the answer of Dr. Perry to my letter, published with his in the *Journal* of January 17, 1952, criticizing the treatment of his two cases reported in the issue of November 29, 1951, under the title "Hypopotassemia in Diabetic Coma," permit me to quote from the paragraph he

suggested be reread: "Possibly both the patients should have received more insulin earlier."

Since, according to the two tables he presented, neither patient received more than 80 units of insulin during the first three hours and since the urines of both patients constantly showed ++++ tests for both glucose and acetone for at least seven hours and for acetone for twelve hours, there can be no doubt that they were treated inadequately with insulin.

Surely, in such an emergency as that presented by diabetic coma, symptomatic treatment dependent on laboratory tests with resulting delays and even dubious significance or importance should not be allowed to interfere with the prompt and intensive administration of sufficient insulin to correct the metabolic disturbances as simply and quickly as possible.

From these two cases, with a 50 per cent mortality, no positive conclusion seems warranted.

GILBERT W. HAIGH, M.D.

Worcester, Massachusetts

To the Editor: The two cases reported by Perry and Rosenbaum in their article entitled "Hypopotassemia in Untreated Diabetic Coma," which appeared in the *Journal* of November 29, 1951, proved to be very instructive indeed.

On January 17, 1952, Dr. Haigh's letter to the editor appeared in the *Journal;* he criticized the inadequate amounts of insulin used by Drs. Perry and Rosenbaum. In the same issue of the *Journal* Dr. Perry replied, stating that the point of the paper was "to emphasize the importance of the routine parenteral use of potassium in diabetic coma after hydration has been started and urinary output is adequate." Nevertheless, the data presented in their article contained several impressive points, and it is a matter of personal choice which point or points should be considered most worthy of emphasis. Actually I was far more impressed by their general method of treatment of diabetic coma, which tended to perpetuate the very condition they strove to alleviate, namely, hypopotassemia.

For the most part, the comments I will make below apply to their first patient, a twenty-two-year-old Negro woman with a serum potassium on admission of 2.3 milliequiv. per liter that fell to 1.07 milliequiv. per liter twenty-four hours later, just before death. The following points are most instructive:

Too little insulin was given early in treatment. At the end of three hours only 80 units had been given and the blood sugar was essentially unchanged. Insulin, if given adequately and vigorously, rapidly reduces potassium wastage into the urine. *Only* insulin will do this. The amount of insulin given in the first one to two hours (not twenty-four hours) is decisive, therefore, in combatting further potassium depletion.

In the presence of a *falling serum potassium* this patient received large amounts of glucose intravenously and additional insulin during the last twelve hours. This practice will not only increase glycosuria (as it did in this case) but also will certainly shift a significant amount of potassium from the serum into the cells. Actually, this procedure is used to lower the serum potassium intentionally in some cases of hyperpotassemia.

Glycosuria persisted throughout the period of treatment and was ++++ at the last examination. Glycosuria delays dehydration and encourages potassium loss.

In general the same criticisms apply to their second case, for at the end of sixteen and one-half hours the blood sugar was higher than it had been on admission!

It should be remembered that diabetic coma is the direct outcome of acute insulin insufficiency and that potassium depletion is, for the most part, a secondary phenomenon. Obviously, then, the main aim of therapy is to correct the basic defect — hypoinsulinism. If this is not done, potassium loss continues unabated and larger amounts of potassium are needed in therapy. Furthermore, the ill-timed intravenous use of glucose, particularly in inordinate amounts, will only make matters worse.

There is no question that these patients needed potassium. However, potassium losses and needs can be diminished if treatment is directed at the underlying insulin deficiency. Unless this is accomplished, one is missing a cardinal point in the treatment of diabetic coma.

ROBERT D. STORY, M.D.
New England Deaconess Hospital

Boston, Massachusetts

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Praktischer Leifaden der beruflichen Hautkrankheiten: unter Berücksichtigung der III and IV. Verordnung über Ausdehnung der Unfallversicherung auf Berufskrankheiten vom. 16 Dezember 1936 und 29 Januar 1943. Von Prof. Dr. Med. C. Carrié. 8°, cloth, 186 pp., with 3 illustrations. Stuttgart: Georg Thieme, 1951. DM 22. Distributed by Grune and Stratton, New York.

This practical manual on occupational skin diseases is well written and the material is well organized. There is a valuable table of methods for determining the toxicity of many substances used in industry. The text is concluded with a bibliography of 288 titles, and there is a good index. The book is well published.

The Pharmacologic Principles of Medical Practice: A textbook on pharmacology and therapeutics for medical students, physicians, and the member of the professions allied to medicine. By John C. Krantz, Jr., professor of pharmacology, University of Maryland School of Medicine, and secretary of the General Committee of Revision of the United States Pharmacopeia 1940–1950, and C. Jelleff Carr, associate professor of pharmacology, University of Maryland School of Medicine, and auxiliary member of the Revision Committee of the United States Pharmacopeia 1940–1950. Second edition. 8°, cloth, 1116 pp., with 95 illustrations and 66 tables. Baltimore: The Williams and Wilkins Company, 1951. $10.00.

In this second edition of a standard treatise first published in 1949, the authors have made extensive revisions throughout the text. Two new chapters have been added, on the chemotherapy of tuberculosis and of rickettsial diseases. New chapters have been added on antimotion-sickness drugs, the treatment of the arthritides and the adrenal corticotrophic hormone and cortisone. The text has been brought in accord with the latest editions of the *United States Pharmacopeia*, the *National Formulary* and *New and Nonofficial Remedies*. The book has enjoyed an unusual popularity, as is evidenced by the need of 5 reprintings of the first edition. The publishing is well done and there is a comprehensive index. The volume is recommended for all reference collections on pharmacology.

The Physiology of the Newborn Infant. By Clement A. Smith, M.D., associate professor of pediatrics, Boston Lying-in Hospital and Harvard Medical School. Second edition. 8°, cloth, 348 pp., with 44 illustrations and 49 tables. Springfield, Illinois: Charles C Thomas, 1951. $7.50.

In this new edition of a special monograph, first published in 1945, the author has made many corrections and has embodied suggestions made by various readers. Lists of references are appended to the various chapters, and there is a good index. The book is recommended to all medical librarians and to all pediatricians.

NOTICES

RHEUMATIC FEVER FELLOWSHIP

The United States Children's Bureau has made available, through the Massachusetts Department of Public Health and the Harvard Medical School, a fellowship in rheumatic fever at the House of the Good Samaritan of the Children's Medical Center, Boston, for the year beginning July 1, 1952.

The trainee should be interested in working eventually in the field of rheumatic fever in public health or in teaching, rather than in private practice. Work under this fellowship will probably be acceptable for credit by the Board of Internal Medicine or the Board of Pediatrics. Application should be made to Dr. Benedict F. Massell at the House of the Good Samaritan, 25 Binney Street, Boston 15. (Telephone BE 2-7800.)

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The Boston City Hospital House Officers' Association will present the following programs in its Evening Lecture Series.

March 25. "Heterologous Transplantation as a Research Tool," by Dr. Harry S. Greene, professor of pathology, Yale University School of Medicine.

April 1. "Mechanical Aspects of Urine Formation in Health and Disease," by Dr. Stanley E. Bradley, associate professor of medicine, Columbia University School of Medicine. Discussers: Drs. William B. Schwartz and John P. Merrill.

April 10. "The Problem of Food Intoxications, with Special Reference to Botulism," by Dr. Karl S. Meyer, professor of experimental pathology, University of California Medical School. Discussers: Drs. David D. Rutstein and Roy F. Feemster.

April 15. "Investigative Studies with Local Use of Steroids, with Special Reference to Compound F," by Dr. Leon Goldman, professor of dermatology, University of Cincinnati College of Medicine. Discussers: Drs. W. F. Lever, W. R. Hill and J. G. Downing.

These programs will be held at 7:00 p.m. in the New Cheever Amphitheatre of the Dowling Building at Boston City Hospital. All interested persons are invited to attend.

BOSTON CITY HOSPITAL ALUMNI ASSOCIATION

On April 26 the Boston City Hospital Alumni Association will present clinics in medicine, surgery, orthopedics and ophthalmology and otolaryngology. These sessions will be held from 8:30 a.m. to 1:00 p.m.

NEW ENGLAND DIABETES ASSOCIATION

The next clinical meeting of the New England Diabetes Association will be held on Friday, March 21, at 8:00 p.m., in the Joslin Auditorium of the New England Deaconess Hospital. Dr. John P. Peters of Yale University will read a paper on "Diabetic Acidosis." Discussers will be Drs. Howard F. Root and Reed Harwood.

All interested persons are invited to attend.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The New England Society of Anesthesiologists will present a program on "The Physiology of the Metabolic System and Its Relation to Anesthesia" on April 5, as part of its Postgraduate Education Program.

PROGRAM

Renal Physiology as Related to Anesthesia — Dr. William B. Schwartz, New England Medical Center.

Adrenal Physiology as Related to Anesthesia — Dr. Dave H. Solomon, research fellow in endocrinology, New England Medical Center.

MASSACHUSETTS TRUDEAU SOCIETY

The Massachusetts Trudeau Society will hold its winter meeting on Thursday, March 27, at 8:20 p.m. at the Boston Medical Library, 8 Fenway, Boston. Dr. Harriet L. Hardy, associate physician at the Occupational Medical Clinic of Massachusetts General Hospital, will speak on "The Clinical Syndrome Associated with Exposure to Beryllium."

Dr. George W. Wright, director of the Physiology Laboratory of the Trudeau Foundation at Saranac, New York, will discuss "Alterations of Pulmonary Function Due to Exposure to Beryllium Compounds."

Physicians and medical students are invited to attend.

AMERICAN CONGRESS OF PHYSICAL MEDICINE

The 30th annual scientific and clinical session of the American Congress of Physical Medicine will be held August 25-29, at the Roosevelt Hotel, New York. All sessions will be open to members of the medical profession in good standing with the American Medical Association. Full information may be obtained by writing to the American Congress of Physical Medicine, 30 North Michigan Avenue, Chicago 2, Illinois.

AMERICAN ACADEMY OF DENTAL MEDICINE

The 6th annual meeting of the American Academy of Dental Medicine will be held at the Mount Royal Hotel, Montreal, Canada, on Thursday, Friday and Saturday, May 29, 30 and 31. All members and interested dentists and physicians are cordially invited to attend. Full details as well as reservations for registrants and their families are available through Dr. William M. Greenhut, 124 East 84th Street, New York 28, N. Y.

SOCIETY MEETINGS AND CONFERENCES

MARCH 21. New England Diabetes Association. Notice above.

MARCH 22–29. Springfield Hospital. Page 316, issue of February 21.

MARCH 23, 28 AND 29. Massachusetts Association of Medical Technologists, Inc. Page 354, issue of February 28.

MARCH 24. Annual Lecture of Sigma (Temple) Chapter of Phi Delta Epsilon Fraternity. Page 316, issue of February 21.

MARCH 24–27. American Academy of General Practice. Page 354, issue of February 28.

MARCH 24–28. American College of Chest Physicians. Page 160, issue of January 24.

MARCH 24–28. Measurement of Pulmonary Function in Health and Disease. American Trudeau Society. Boston Medical Library.

MARCH 24–APRIL 30. Seventh Postgraduate Lecture Course. Page 274, issue of February 14.

MARCH 25–APRIL 15. Boston City Hospital. House Officers' Association. Notice above.

MARCH 25 AND APRIL 24. Norfolk District Medical Society. Page 710, issue of November 1.

MARCH 26. Boston Gastroenterological Society. Page 354, issue of February 28.

MARCH 26. Lahey Clinic. Fellowship Teaching Program. Page 160, issue of January 24.

MARCH 27. Alcoholism Staff Conference. Quincy City Hospital. 1:30–3:00 p.m.

MARCH 27. Massachusetts Trudeau Society. Notice above.

MARCH 29 AND 30. American Psychosomatic Society. Page 390, issue of March 6.

MARCH 31–APRIL 4. Fifth American Congress on Obstetrics and Gynecology. Page 832, issue of November 22.

APRIL 2. Tufts Medical Alumni Association. Page 354, issue of February 28.

APRIL 2–30. Springfield Hospital. Page 433, issue of March 13.

APRIL 3–5. Frank E. Bunts Educational Institute. Page 434, issue of March 13.

APRIL 5 AND MAY 3. New England Society of Anesthesiologists. Postgraduate Education Course. Page 996, issue of December 20 and notice above.

APRIL 7–9. American College of Allergists. Page 390, issue of March 6.

APRIL 10. Mistakes in Diagnosis of Angina Pectoris and Coronary Occlusion. Dr. Howard B. Sprague. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

APRIL 14–25. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

APRIL 15. Massachusetts Society for Research in Psychiatry. Page 792, issue of November 15.

APRIL 17–19. Boston Lying-in Hospital and Children's Hospital. Postgraduate Course in Obstetrics and Pediatrics. Page 433, issue of March 13.

APRIL 21–25. Cancer Seminar. Page 114, issue of January 17.

APRIL 23. Massachusetts Academy of General Practice. Springfield.

APRIL 23. New England Obstetrical and Gynecological Society (Spring Meeting). Hartford, Connecticut.

APRIL 25 AND 26. Texas Medical Center. Page 354, issue of February 28.

APRIL 26. Boston City Hospital Alumni Association. Notice above.

APRIL 26. Alumni Association of the Long Island College of Medicine. Page 434, issue of March 13.

MAY 3. Annual Meeting. Massachusetts Association of Medical Technologists, Inc. Page 433, issue of March 13.

MAY 10. Boston Dispensary Proctologic Session. Page 433, issue of March 13.

MAY 10 AND 11. American Electroencephalographic Society. Page 390, issue of March 6.

MAY 11–17. Pan-American Convention of Gastroenterology. Page 434, issue of March 13.

MAY 19–23. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

MAY 20–22. Massachusetts Medical Society. Hotel Statler, Boston.

MAY 26–28. Minnesota State Medical Association. Annual Meeting. Page 316, issue of February 21.

MAY 26–29. National Tuberculosis Association. Copley Plaza and Statler hotels, Boston.

MAY 29–31. American Academy of Dental Medicine. Notice above.

JUNE 5–8. American College of Chest Physicians. Page 280, issue of February 14.

JUNE 18–20. Massachusetts Public Health Conference. Amherst.

JUNE 22–26. American Society of Technologists. Twentieth Annual Convention, Portland, Oregon.

(Notices concluded on page xiii)